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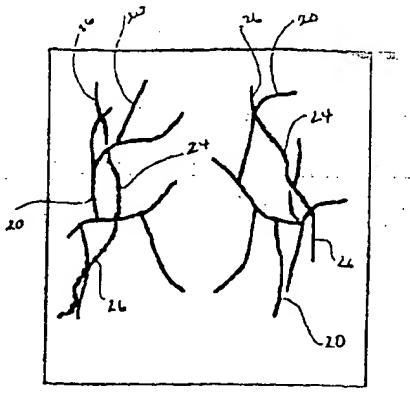
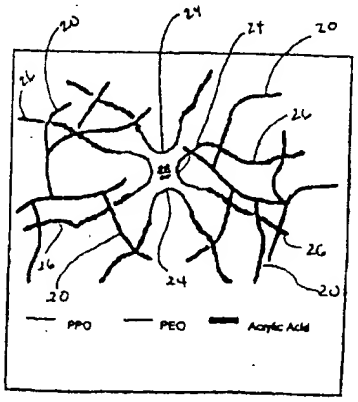
(57) Abstract

A pharmaceutic composition includes a pharmaceutically acceptable carrier, comprising a reverse thermally viscosifying polymer network. The polymer network includes at least one responsive polymer component, said responsive component capable of aggregation in solution in response to an environmental stimulus and at least one structural component, said structural component exhibiting self-repulsive interactions over use conditions. The responsive component is randomly bonded to said structural component and the polymer network characterized in that it viscosifies in response to said environmental stimulus. The composition further includes a pharmaceutically active agent which imparts a pharmaceutic effect, said carrier and said agent disposed within an aqueous-based medium. The composition is suitable for administration of the pharmaceutical agent across dermal, otic, rectal, vaginal, ophthalmic, esophageal and nasal mucosal membranes.





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COMPOSITION FOR PHARMACEUTICAL APPLICATIONS

This application is a continuation-in-part application of copending application PCT/US96/10376 filed June 14, 1996, designating the United States, and entitled "Responsive Polymer Networks and Methods of Their Use", which is a continuation-in-part application of copending application U.S.S.N. 08/580,986 filed January 3, 1996, and entitled "Responsive Polymer Networks and Methods of Their Use", each of which is incorporated entirely by reference.

This application claims priority under 35 U.S.C. §119(e) to United States Provisional Application 60/023,996, filed August 12, 1996, entitled "Drug Delivery System", United States Provisional Application 60/025,974 filed September 16, 1996, entitled "Modification of Rheological Properties of Reverse Thermoviscosifying Gels", United States Provisional Application 60/028,183, filed October 15, 1996, entitled "Shifts in Transition Temperature of Smart Hydrogel", United States Provisional Application 60/030,798, filed November 14, 1996, entitled "Associative Thickeners Based on Smart Hydrogel", United States Provisional Application 60/034,454, filed January 2, 1997, entitled "Responsive Polymer Networks and Methods of Their Use: Thermal Stabilization", and United States Provisional Application 60/034,174, filed January 2, 1997, entitled "Delivery of Peptides in Sheep", which are hereby incorporated in its entirety by reference.

Field of the Invention

The present invention relates to pharmaceutic compositions useful in a variety of pharmaceutical products and applications, and in particular, compositions useful transmucosal applications, such as esophageal, otic, vaginal, rectal, topical and ophthalmic. More particularly, the present invention is directed to a pharmaceutic composition for treating a disease or disorder comprising a polymer network that can be designed to reversibly gel over a wide range of conditions.

Background of the Invention

One of the major concerns in the delivery of drugs is the bioavailability of the drug. Depending upon the nature of the drug and the route of delivery the bioavailability may be very low due to, for example, the degradation of oral-delivered drugs by hepato-gastrointestinal first-pass elimination or rapid clearance of the drug from the site of application. The net result is that frequent dosing may be required with higher than needed amounts of drug, which can lead to undesired side effects. Thus, it is desired by the pharmaceutical industry to have ways of administering drugs such that their availability can be controlled in an even dosing manner, the amounts of drugs can be kept as low as possible to minimize side effects, and dosing regime can be kept to a minimum to provide greater convenience to the subject, thus promoting greater compliance with appropriate dosing.

Many instances are known in the pharmaceutic industry where it is desired to have certain properties of viscosity in order to facilitate the objectives noted above. Hydrogels, such as cellulosics, have been included as thickeners in pharmaceutic compositions. A hydrogel is a polymer network which absorbs a large quantity of water without the polymer dissolving in water. The hydrophilic areas of the polymer chain absorb water and form a gel region. The extent of gelation depends upon the volume of the solution which the gel region occupies.

Reversibly gelling solutions are known in which the solution viscosity increases and decreases with an increase and decrease in temperature, respectively. Such reversibly gelling systems are useful wherever it is desirable to handle a material in a fluid state, but performance is preferably in a gelled or more viscous state.

A known material with these properties is a thermal setting gel using block copolymer polyols, available commercially as Pluronic® polyols (BASF, Ludwigshafen, Germany), which is described in U.S. Patent No. 4,188,373. Adjusting the concentration of the polymer gives the desired liquid-gel transition. However, concentrations of the polyol polymer of at least 18-20 % by weight are needed to produce a composition which exhibits such a transition at commercially or physiologically useful temperatures. Also, solutions containing 18-20 % by weight of

responsive polymer are typically very viscous even in the "liquid" phase, so that these solutions can not function under conditions where low viscosity, free-flowing is required prior to transition. In addition, these polymer concentrations are so high that the material itself may cause unfavorable interactions during use.

Another known system which is liquid at room temperature, but forms a semi-solid when warmed to about body temperature is formed from tetrafunctional block polymers of polyoxyethylene and polyoxypropylene condensed with ethylenediamine, commercially available as Tetronic® polyols. These compositions are formed from approximately 10% to 50% by weight of the polyol in an aqueous medium. See, U.S. Patent No. 5,252,318.

Joshi *et al.* in U.S. Patent No. 5,252,318 reports reversible gelling compositions which are made up of a physical blend of a pH-sensitive gelling polymer (such as a cross-linked poly(acrylic acid) and a temperature-sensitive gelling polymer (such as methyl cellulose or block copolymers of poly(ethyleneoxide) and poly(propyleneoxide)). In compositions including methylcellulose, 5- to 8-fold increases in viscosity are observed upon a simultaneous change in temperature and pH for very low methylcellulose levels (1-4% by weight). See, Figs. 1 and 2 of Joshi *et al.* In compositions including Pluronic® and Tetronic® polyols, commercially available forms of poly(ethyleneoxide)/poly(propyleneoxide) block copolymers, significant increases in viscosity (5- to 8-fold) upon a simultaneous change in temperature and pH are observed only at much higher polymer levels. See, Figs. 3-6 of Joshi *et al.*

Hoffman *et al.* in WO 95/24430 disclose block and graft copolymers comprising a pH-sensitive polymer component and a temperature-sensitive polymer component. The block and graft copolymers are well-ordered and contain regularly repeating units of the pH-sensitive and temperature-sensitive polymer components. The copolymers are described as having a lower critical solution temperature (LCST), at which both solution-to-gel transition and precipitation phase transition occur. Thus, the transition to a gel is accompanied by the clouding and opacification of the solution.

Light transmission is reduced, which may be undesirable in many applications, where the aesthetic characteristics of the composition are of some concern.

Thus, the known systems which exhibit reversible gelation are limited in that they require large solids content and/or in that the increase in viscosity less desired. In addition, some known systems exhibit an increase in viscosity which is accompanied with the undesirable opacification of the composite.

Summary of the Invention

It is an object of the present invention to provide a pharmaceutic composition which includes a component capable of reversible gelation or viscosification.

It is a further object of the invention to provide a pharmaceutic composition which includes an component capable of gelation or viscosification at very low solids content.

It is another object of the present invention to provide a pharmaceutic composition which possesses improved flow and gelation characteristics as compared to properties possessed by conventional reversible gelation compositions.

It is a further object of the invention to provide a polymer network composition for use in pharmaceutic compositions as a surfactant or emulsifier in the solubilization of additives and, in particular, hydrophobic additives, and desirably to provide stable emulsions at elevated temperatures.

It is a further object of the invention to provide a pharmaceutic composition which possesses the appropriate thickness for sustained delivery and pharmaceutic effect with a minimum of solids content.

It is a further object of the invention to provide a polymer network for use in pharmaceutic compositions as a suspension agent for otherwise insoluble additives.

It is yet another object of the present invention to provide reversibly gelling polymer network compositions which are composed of biocompatible polymers.

These and other objects of the invention are achieved in a pharmaceutic composition comprising a reversibly gelling polymeric network for the delivery of drugs. New ways of delivering drugs at the right time, in a controlled manner, with

minimal side effects, and greater efficacy per dose are continually sought by the drug delivery and pharmaceutical industries. The reversibly gelling polymeric network of this invention has the physico-chemical characteristics that make it a suitable drug delivery vehicle for transmucosal delivery of conventional small chemical drugs as well as new macromolecular (e.g., peptides) drugs or therapeutic products.

The reversibly gelling polymer network comprises a responsive polymer component capable of aggregation in response to an environmental stimulus. The responsive polymer component is randomly bonded to a structural polymer component which exhibits self-repulsive interactions over the use conditions of the pharmaceutical composition. The repulsive forces cause the structural component to remain extended and solvated in an aqueous medium. The reversibly gelling polymer network is characterized in that it viscosifies in response to the environmental stimulus. The polymer network may also include some unbound or "free" responsive polymer or other additives which contribute to or modify the characteristic properties of the polymer composition.

In addition, the pharmaceutic composition includes a pharmaceutic agent selected to provide a preselected pharmaceutic effect. A pharmaceutic effect is one which seeks to treat the source or symptom of a disease or physical disorder. Pharmaceutics include those products subject to regulation under the FDA pharmaceutic guidelines, as well as consumer products.

By "gelation" or "viscosification" as those terms are used herein, it is meant a drastic increase in the viscosity of the polymer network solution. Gelation is dependent on the initial viscosity of the solution, but typically a viscosity increase at pH 7 and 1 wt% polymer concentration is in the range of preferably 2- to 100-fold, and preferably 5- to 50-fold, and more preferably 10- to 20-fold for a polymer network which is used in the preparation of the pharmaceutic compositions of the invention. Such effects are observed in a simple polymer network solution and the effect may be modified by the presence of other components in the pharmaceutic composition.

By "reversibly gelling" as that term is used herein, it is meant that the process of gelation takes place upon an *increase* in temperature rather than a decrease in temperature. This is counter-intuitive, since solution viscosity typically *decreases* with an increase in temperature.

By "use conditions" as that term is used herein it is meant all conditions to which the composition is likely to be exposed during its use, including during shipment and storage as well as during medical treatment.

The novel interaction between the constituent polymers components of the reversibly gelling polymer network permits formation of gels at very low solids content. Gelation and/or viscosification is observed in aqueous solutions having about 0.01 to 20 wt% of the responsive polymer component and about 0.01 to 20 wt% of the structural polymer component. A typical reversibly gelling polymer network may be comprised of about 0.01 wt% to about 10 wt%, preferably less than about 4 wt% of total polymer solids (e.g., responsive polymer and structural polymer), and more preferably less than 1 wt% total polymer solids, while still exhibiting reverse thermal viscosification. Of course, the total solids content of the composition, including additives and the pharmaceutic agent, may be much higher. The viscosity of a 1 wt% polymer network increases at least ten-fold with an increase in temperature of about 5°C at pH 7. Viscosity increases may be even greater over a larger temperature range at pH 7 and or higher polymer network content.

The relative proportion of responsive polymer and structural polymer may vary in the composition, dependent upon the desired properties of the pharmaceutic composition. In one embodiment, the responsive polymer is present in a range of about 1 to 20 wt% and the structural polymer is present in a range about of 99 to 80 wt%. In another embodiment, the responsive polymer component is present in a range of about 21 to 40 wt% and the structural polymer component is present in a range of about 79 to 60 wt%. In another embodiment, the responsive polymer component is present in a range of about 41 to 50 wt% and the structural polymer component is present in a range of about 59 to 50 wt%. In another embodiment, the responsive polymer component is present in a range of about 51 to 60 wt% and the

structural polymer component is present in a range of about 49 to 40 wt%. In yet another embodiment, the responsive polymer component is present in a range of about 61 to 90 wt% and the structural polymer component is present in a range of about 39 to 20 wt%. In another embodiment, the responsive polymer component is present in a range of about 81 to 99 wt% and the structural polymer component is present in a range of about 19 to 1 wt%.

The reversibly gelling polymer network described above may be included in a pharmaceutic composition as a delivery vehicle for a pharmaceutic agent. In addition, the reversibly gelling polymer network may be included to improve the flow characteristics, thickness and other properties of the composition. Additives also may be included to modify the polymer network performance, such as to increase or decrease the temperature of the liquid-to-gel transition and/or to increase or decrease the viscosity of the responsive polymer composition.

In one aspect of the invention, the reversibly gelling polymer network is incorporated into a pharmaceutic composition to impart thickening properties to the composition at the use and/or application temperature. Such thickening properties include enhanced overall viscosity, as well as a desirable viscosity response with temperature. The polymer network may be useful as a thickener in pH ranges where other thickeners are not effective.

In another aspect of the invention, the reversibly gelling polymer network is incorporated into a pharmaceutic composition to stabilize and solubilize hydrophobic agents in the pharmaceutic composition. The reversibly gelling polymer network may be included to increase emulsion stability. Many emulsions (a suspension of small droplets or particles of a first material in a second material) lose viscosity upon heating. As will be demonstrated herein, the reversibly gelling polymer network retains its emulsifying properties even at elevated temperatures.

In addition, the reversibly gelling polymer network may be included in the composition to impart emolliency to the composition. The composition may also act as a film-forming agent after it has been applied to the skin or other mucosal membrane. This film-forming agent may be used as a barrier to prevent water loss

from the skin which contributes to the moisturization of the skin. The formed-film could also provide protective coating ("band-aid") to protect the tissue against environmental challenge(s) or to provide a mechanical separation between to adjust tissues (adhesion prevention).

Brief Description of the Drawing

The invention is described with reference to the Drawing, which is presented for the purpose of illustration and is in no way intended to be limiting, and in which:

Figure 1 is a schematic illustration of the poloxamer:poly(acrylic acid) polymer network below and above the transition temperature illustrating the aggregation of the hydrophobic poloxamer regions;

Figure 2 is a graph of viscosity vs. temperature for a 1 wt%, 2 wt% and 3 wt% responsive polymer network aqueous composition of a poloxamer/poly(acrylic acid) (1:1) at pH 7.0 measured at a shear rate of 0.44 sec^{-1};

Figure 3 is a graph of viscosity vs. temperature for a 1 wt% poloxamer: poly(acrylic acid) polymer network composition demonstrating reversibility of the viscosity response;

Figure 4 shows the viscosity response of a 2 wt% poloxamer:poly(acrylic acid) polymer composition at various shear rates;

Figure 5 shows a viscosity response curve for a 2 wt% poloxamer: poly(acrylic acid) polymer network composition prepared with nominal mixing and stirring and prepared using high shear homogenization (8000 rpm, 30 min);

Figure 6 is a graph of viscosity vs. temperature for a 1 wt% poloxamer: poly(acrylic acid) polymer network composition at various pHs;

Figure 7 is a graph of viscosity vs. temperature for a 1 wt% poloxamer: poly(acrylic acid) polymer network composition with and without addition of 0.25 wt% KCl;

Figure 8 is a graph of viscosity vs. temperature for a 1 wt% poloxamer: poly(acrylic acid) polymer network composition with and without addition of 0.5 wt% acetamide MEA;

Figure 9 is a graph of viscosity vs. temperature for a 1 wt% poloxamer: poly(acrylic acid) polymer network composition without and with 5 wt%, 10 wt% and 20 wt% added ethanol, respectively;

Figure 10 is a graph of viscosity vs. temperature for a 1 wt% poloxamer: poly(acrylic acid) polymer network composition without and with addition of 0.025 wt% Surfynol CT11;

Figure 11 is an illustration of a reversibly gelling polymer network used as an emulsifier and stabilizer for a hydrophobic agent;

Figure 12A is a plot of equilibrium solubility of estradiol in aqueous (pH 7.0) solutions of a reversibly gelling polymer network and Figure 10B a plot of the release of estradiol from the polymeric composition as a function of concentration;

Figure 13A plot of equilibrium solubility of progesterone in aqueous (pH 7.0) solutions of a reversibly gelling polymer network and Figure 11B a plot of the release of progesterone from the polymeric composition as a function of concentration;

Figure 14 is a plot of viscosity vs. temperature for (a) a 1 wt% responsive polymer network aqueous composition of Pluronic® F127 poloxamer/poly(acrylic acid) (1:1) and (b) a 1 wt% physical blend of Pluronic® F127 poloxamer/poly(acrylic acid) (1:1) at pH 7.0 measured at a shear rate 0.22 sec^{-1};

Figure 15 is a plot of viscosity vs. temperature for a 1 wt% responsive polymer network aqueous composition of Pluronic® F88 poloxamer/poly(acrylic acid) (1:1) at pH 7.0 measured at a shear rate 2.64 sec^{-1};

Figure 16 is a graph of the viscosity vs. temperature effect for a responsive polymer network composition of 2 wt% Pluronic® P104 poloxamer/poly(acrylic acid) (1:1) in deionized water at pH 7.0 measured at shear rate of 22 sec^{-1};

Figure 17 is plot of viscosity vs. temperature for a responsive polymer network composition of 2 wt% Pluronic® F123 poloxamer/poly(acrylic acid) (1:1) at pH 7.0 measured at a shear rate of 22 sec^{-1};

Figure 18 is plot of viscosity vs. temperature for a responsive polymer network composition of 2 wt% Pluronic® F127/poly(acrylic acid-*co*-methacrylic acid) (1:1) in deionized water at a shear rate of 22 sec^{-1};

Figure 19 is a plot of viscosity vs. temperature for 1 wt% made of series of poloxamers and poly(acrylic acid) (1:1) in deionized water at a shear rate of 132 sec^{-1};

Figure 20 is a plot of viscosity vs. temperature for a responsive polymer network composition of a 2 wt% polyethyleneglycol mono(nonylphenylether)/ polyacrylic acid (1:1) at pH 7.0 at a shear rate of 2.64 sec^{-1};

Figure 21 is a plot showing release of hemoglobin from a poloxamer/poly(acrylic acid) polymer network of the invention;

Figure 22 is a plot showing the release of lysozyme from the poloxamer/poly(acrylic acid) polymer complex of the invention;

Figure 23 is a plot showing release of insulin from a poloxamer/poly(acrylic acid) polymer network composition of the invention;

Figure 24 is a plot of viscosity vs. temperature for a poloxamer/poly(acrylic acid) polymer network composition (a) before and (b) after sterilization by autoclave;

Figure 25 is a plot of the effect of loading fluorescein on the onset of gelation of responsive polymer network vs. total polymer concentration in responsive polymer network solution (pH 7.0);

Figure 26 is a plot of the rate of progesterone release and macroscopic viscosity vs. polymer concentration;

Figure 27 is a plot of the percentage of progesterone release vs. polymer concentration in responsive polymer network;

Figure 28 is a plot of fluorescein retention in rabbit eye vs. time for a 1 wt% poloxamer:poly(acrylic acid) polymer network;

Figure 29 is a scintigraphic assessment of corneal residence time in human and rabbit eyes, which compares residence time for a poloxamer:poly(acrylic acid) composition with that of commercially available materials;

Figure 30 is a plot of activity vs. time to determine retention time of a nasal composition of the invention in the nasal passages;

Figure 31 is a plot of serum concentration of luteinizing hormone in sheep administered nasally from a 5.5 wt% solution of a poloxamer:poly(acrylic acid) polymeric network containing 100 μg of a GnRH analog;

Figure 32 is a plot of activity vs. time to determine retention time of a nasal composition of the invention in the esophageal passages;

Figure 33 is a plot of cumulative serum estradiol levels vs. time following vaginal delivery of estrogens in sheep using a poloxamer:poly(acrylic acid) polymeric delivery vehicle; and

Figure 34 is a plot of serum luteinizing hormone levels vs. time following vaginal delivery of GnRH and its analogs in sheep using a poloxamer:poly(acrylic acid) polymeric delivery vehicle.

Detailed Description of the Invention

The present invention is directed to a pharmaceutic composition comprising a novel responsive component:structural component polymer network. The polymer network functions as an environmentally sensitive thickening agent, and in addition possesses surfactant and emulsifying capabilities which may be beneficial to the pharmaceutic composition. The polymer network composition according to the invention includes a responsive polymer component randomly covalently bonded to a structural polymer component. The polymer network contains about 0.01-20 wt% each of responsive polymer and structural polymer. Exemplary polymer network compositions range from about 1:10 to about 10:1 responsive polymer:structural polymer. Polymer network gel compositions which exhibit a reversible gelation at body temperature (25-40°C) and/or at physiological pH (ca. pH 3.0-9.0) and even in basic environments up to pH 13 (e.g., the gasto-intestinal environment) are particularly preferred for pharmaceutic applications.

The compositions of the invention include a safe and effective amount of a pharmaceutically active agent. "Safe and effective", as it is used herein, means an amount high enough to significantly positively modify the condition to be treated or the pharmaceutic effect to be obtained, but low enough to avoid serious side effects.

The responsive component is an oligomer or polymer which will respond to a stimulus to change its degree of association and/or agglomeration. The stimulus may be temperature, pH, ionic concentration, solvent concentration. light. magnetic field,

electrical field, pressure or other triggers commonly used to trigger a responsive gel material. Temperature is a preferred environmental trigger. The aggregation may be in the form of micelle formation, precipitation, labile crosslinking or other factors.

The responsive component typically possesses regions of hydrophobic character, e.g., poly(propyleneoxide) blocks, and hydrophilic character, e.g., poly(ethyleneoxide) blocks in order to facilitate aggregation. The responsive polymer may be linear or branched. Suitable responsive components include polyoxyalkylene polymers, such as block copolymers of different oxyalkylene units. At least one polyoxyalkylene unit should have hydrophobic characteristics and at least one polyoxyalkylene unit should have hydrophilic characteristics. A block copolymer of polyoxyethylene and polyoxypropylene may be used in a preferred embodiment of the invention. Another suitable responsive component includes poloxamers, which are triblock polyol polymers having the general of a triad ABA block copolymer, $(P_1)_a(P_2)_b(P_1)_a$, where P_1 = poly(ethyleneoxide) and P_2 = poly(propyleneoxide) blocks, where a is in the range of 10-50 and where b is in the range of 50-70. Pluronic® (BASF) triblock polymers are commercially available for *a* in the range of 16 to 48 and *b* ranging from 54-62.

Other exemplary polyoxyalkylene polymers include alkyl polyols, which are a product of alcohol condensation reactions with a terminal alkyl or arylalkyl group. The alkyl group should have hydrophobic character, such as butyl, hexyl and the like. An alkyl polyol may have the general formula $R\text{-}(OCH_2CH_2)_nOH$, where R is a nonpolar pendant group such as alkyl and arylalkyl and the like, and n is in the range of 5-1000. A preferred alkylpolyol is polyethyleneglycol mono(nonylphenyl)ether. Still other exemplary responsive components may include cellulosic, cellulose ethers and guar gums which possess hydrophobic and hydrophilic regions along the polymer backbone which permit aggregation behavior. One or more responsive components may be used in the reversibly gelling polymer network composition of the present invention.

The structural component is an oligomer or polymer which serves as a support for the responsive polymer so that a multi-component polymer network is formed. The structural component experiences self-repulsive interactions, that is, the structural

polymer tends to repel rather than attract like structural polymer components. This results in an extended structural polymer. The structural component exhibits such repulsive interactions over the entire use conditions of the polymer network. Thus, unlike the responsive component of the polymer network which exists in two different states, e.g., aggregated and non-aggregated, dependent upon its environment, the structural component remains in a substantially extended over the entire use condition of the composition.

Suitable structural components include ionizable polymers. Ionization provides the repulsive self-interactions which characterize the structural polymer component. The ionizable polymers of the present invention include linear, branched and/or crosslinked polymers. Of particular interest are carboxyvinyl polymers of monomers such as acrylic acid, methacrylic acid, ethacrylic acid, phenyl acrylic acid, pentenoic acid and the like. Poly(acrylic acid) and its salts is a preferred carboxyvinyl polymer. One or more poly(carboxyvinyl) polymers may be used in the responsive polymer network compositions of the present invention. Copolymers, such as by way of example only, copolymers of acrylic acid and methacrylic acid, are also contemplated. Naturally occurring polymers such as chitosan or hyaluronic acids are also possible as structural polymers since they are capable of forming an ionized network as polymers or copolymers of other structural polymers.

Non-ionized polymers which contain both hydrophilic and hydrophobic groups may be suitable structural polymers where they exhibit sufficient repulsive forces over use conditions to maintain the polymer extended in solution. Suitable non-ionized structural polymers include, acrylamides or substituted acrylamides.

The poly(acrylic acid) may be linear, branched and/or crosslinked. Poly(acrylic acid) is capable of ionization with a change in pH of the solution. By ionization, as that term is used with respect to poly(acrylic acid), it is meant the formation of the conjugate base of the acrylic acid, namely acrylate. As used herein, poly(acrylic acid) includes both ionized and non-ionized versions of the polymer. Changes in ionic strength may be accomplished by a change in pH or by a change in salt concentration. The viscosifying effect of the polymer network is partly a function of the ionization of

the poly(acrylic acid); however, reverse thermal gelling may occur without ionization. Changes to the ionic state of the polymer causes the polymer to experience attractive (collapsing) or repulsive (expanding) forces. Where there is no need or desire for the composition to be applied in a high viscosity state, it may be possible to prepare the composition as non-ionized poly(acrylic acid). The body's natural buffering ability will adjust the pH of the applied composition to ionize the poly(acrylic acid) and thereby develop its characteristic viscosity.

The reversibly gelling responsive polymer networks compositions of the present invention are highly stable and do not exhibit any phase separation upon standing or upon repeated cycling between a liquid and a gel state. Samples were stored at 45 °C for more than three months without any noticeable decomposition, clouding, phase separation or degradation of gelation properties. This is in direct contrast to polymer blends and aqueous mixed polymer solutions, where phase stability and phase separation is a problem, particularly where the constituent polymers are immiscible in one another.

Without intending to be bound by any particular mechanism or chemical structure, it is believed that the structure of the polymer network involves a random bonding of the responsive polymer component onto the backbone of an extended, well-solvated structural polymer component. The combination of the structural polymer component and randomly bonded responsive polymer component gives the composition its unique properties. Viscosity is a function of the molecular weight of the solubilized polymer. Aggregation of the responsive polymer component increases the effective molecular weight of the polymer network. The aggregation may be in the form of micelle formation, precipitation, labile crosslinking or other factors. The repulsive forces of the structural polymer component keeps the polymer in an extended, solvated state which prevents precipitation upon the effective increase in molecular weight.

With reference to a particular reversibly gelling polymer network, poloxamer:poly(acrylic acid), the observed thermal behavior of the reversibly gelling polymer network suggests that the increase in viscosity is due to aggregation of the

hydrophobic portion of the poloxamer at the transition temperature which, because of bonding with the poly(acrylic acid) component, serve as temporary cross-links which physically bridge adjacent chains of poly(acrylic acid) to provide a viscous gel-like extended polymer structure. The aggregation process may be understood as occurring as shown in Figure 1, in which a backbone 20 represent poly(acrylic acid), a thin band 24 represents the hydrophobic poly(propyleneoxide) region of the poloxamer and a thick band 26 represents the hydrophilic poly(ethyleneoxide) region of the poloxamer. Below the transition temperature, the polymer network is randomly arranged, as is shown in Figure 1A. At or above the transition temperature, the hydrophobic regions 24 associate to form aggregations or micelles 28, as is shown in Figure 1B. The association increases the effective molecular weight of the polymer network composition with the corresponding increase in viscosity.

The reverse viscosification effect at low polymer concentrations provides clear, colorless gels which are particularly well-suited to pharmaceutic applications. For example, very little residue is formed upon dehydration which may be important in some applications, such as in optically applied pharmaceutics. An additional advantage of the polymer network of the invention is that it remains clear and translucent before and after the triggering environmental change. These characteristics of the reversibly gelling polymer network make it well suited for use in pharmaceutic compositions.

The practical advantage of this behavior of the composition is that the formulation can be administered as a flowing liquid at ambient temperatures. Upon contact with body tissues it viscosifies, thus changing its flow properties, and more importantly, its clearance from the site of application. Furthermore, for polymers in general, the viscosity at ambient temperature is concentration dependent. As the concentration is increased to achieve desired flow properties in contact with body tissues, the viscosity at ambient temperatures also increases, making it more difficult to administer such compositions. The uniqueness of the polymeric network of this invention also allows it to the administered easily at ambient temperatures as a flowing

liquid at various concentrations; its gelled state is only realized once it has been placed in contact with body tissues.

Thus, a composition may be prepared at low temperatures while the polymer network is in a low viscosity state. Mixing of ingredients under low viscosity is expected to be easier, thus simplifying the manufacturing process. Yet, the resultant mixture would be of increased viscosity at use temperatures. As a further advantage, a pharmaceutic composition comprising reversibly gelling polymer network may be spread thinly to allow for even application, due to its low viscosity at room temperature, but will thicken and "fill" the body contours upon warming up to body surface temperature.

The reversibly gelling polymer network may also be included in a pharmaceutic composition for use as a stabilizing, solubilizing or emulsifying agent for a hydrophobic component of the pharmaceutic formulation. Upon aggregation and/or micelle formation in the responsive component, hydrophobic domains are created which may be used to solubilize and control release of hydrophobic agents. Similar micelle-based systems have been shown to protect trapped peptides and proteins against enzymatic degradation from surface enzymes.

An example of the dramatic increase in viscosity and of the gelation of the reversibly gelling polymer network compositions of the invention is shown in Figure 2. Figure 2 is a graph of viscosity vs. temperature for 1 wt%, 2 wt% and 3 wt% polymer network compositions comprising 1:1 poloxamer:poly(acrylic acid), hydrated and neutralized. The viscosity measurements were taken on a Brookfield viscometer at a shear rate of 0.44 sec^{-1} at pH 7.0. All solutions had an initial viscosity of about 1080 cP and exhibited a dramatic increase in viscosity to gel point at about 35°C. This is not typical of all polymer network compositions since polymerization condition will affect initial viscosity. Final viscosities were approximately 33,000 cP, 100,000 cP and 155,000 cP for the 1 wt%, 2 wt% and 3 wt% compositions, respectively. This represents viscosity increases of about 30-, 90- and 140-fold, respectively. This effect is entirely reversible. Upon cooling, the composition regains its initial viscosity. This is demonstrated in Figure 3, where a 1 wt% poloxamer:poly(acrylic acid) composition

is warmed through the transition temperature up to 35 °C (simple curve), cooled to room temperature (24 °C, ticked curve) and then warmed again to up above the transition temperature (open box curve). The viscosity response was virtually identical in all three instances.

As would be expected with a non-Newtonian system, the solution viscosity differs with different shear rates. Figure 4A shows the viscosity response of a 2 wt% poloxamer:poly(acrylic acid) polymer composition at various shear rates. The viscosity response is consistent up to 24 °C; however, the final viscosity is reduced with increasing shear rate. At low temperatures, the polymeric network behaves approximately like a Newtonian liquid - very little shear thinning is observed in the available shear range. As the temperature and the viscosity increases, so does the shear thinning. High temperature, high shear rate data can fitted with a power law model, $\eta \propto \gamma^{n-1}$ where η and γ are the viscosity and the shear rate, respectively. The 42 °C date in Figure 4B yield the exponent n=0.9, which indicates extreme shear thinning, since shear stress is almost independent of the shear rate.

However, unlike many prior art hydrogels, e.g., carbomers, the responsive component: structural component polymer network composition does not permanently loose viscosity after being subjected to high shear conditions. The polymer network composition remains unaffected by such shear conditions as homogenization. Figure 5 compares the viscosity response curve of a 2 wt% poloxamer:poly(acrylic acid) polymer composition prepared with nominal mixing (simple line) and stirring with that of a polymer composition of similar composition prepared using high shear homogenization designated by a ticked line (8000 rpm, 30 min). No significant decrease in viscosity is observed.

The practical implication of this effect is that the polymeric network compositions can be delivered even at high temperatures if sufficiently high shear is available. In specific pharmaceutical applications, such as ophthalmic compositions, the shear thinning behavior also allows for the composition to be spread across the precorneal surface of the eye as a result of the shearing effect of the movement of the eyelids. The

composition may also be applied through a nozzle that provides high shear to reduce viscosity, yet the composition regains its viscosity after application to the treatment area. This contrasts with conventional formulations which permanently lose viscosity after being subjected to high shear.

A number of factors influence the viscosity and transition temperature of the composition. The more important factors include polymer concentration, pH and presence and nature of additives.

The effect of pH on the viscosity of reversibly gelling polymer networks is shown in Figure 6 for a 1 wt % poloxamer:poly(acrylic acid) polymer network. Increasing pH from the starting pH has a lesser effect on the viscosity than decreasing the pH. This may relate to the extent of ionization of the poly(acrylic acid) component of the polymer network as discussed above which will affect the strength of repulsive forces in the structural polymer. This may be clearly seen in Figure 6 when comparing the viscosity response at pH 5 and pH 11. Satisfactory viscosities can be obtained at high pHs indicating the potential value of the reversibly gelling polymer network in applications such as in the intestinal tract.

The pharmaceutical composition may also include additives for influencing the performance of the polymer network, such as the transition temperature and the viscosity of the polymer composition above the transition temperature. The following list is not intended to be exhaustive but rather illustrative of the broad variety of additives which can be used.

These materials include solvents (e.g., 2-propanol, ethanol, acetone, 1,2-pyrrolidinone, N-methylpyrrolidinone), salts (e.g., calcium chloride, sodium chloride, potassium chloride, sodium or potassium phosphates, borate buffers, sodium citrate), preservatives (benzalkonium chloride, phenoxyethanol, sodium hydroxymethylglycinate, ethylparaben, benzoyl alcohol, methylparaben, propylparaben, butylparaben, Germaben II), humectant/moisturizers (acetamide MEA, lactimide MEA, hydrolyzed collagen, mannitol, panthenol, glycerin), lubricants (hyaluronic acid, mineral oil, PEG-60-lanolin, PPG-12-PEG-50-lanolin, PPG-2 myristyl ether propionate) and surfactants.

Surfactants may be divided into three classes: cationic, anionic, and nonionics. An example of a cationic surfactant used is ricinoleamidopropyl ethyldimonium ethosulfate (Lipoquat R). Anionic surfactants include sodium dodecyl sulfate and ether sulfates such as Rhodapex CO-436. Nonionic surfactants include Surfynol CT-111, TG, polyoxyethylene sorbitan fatty acid esters such as Tween 65 and 80, sorbitan fatty acid esters such as Span 65, alkylphenol ethoxylates such as Igepal CO-210 and 430, dimethicone copolyols such as Dow Corning 190, 193, and Silwet L7001.

The addition of polymers has been studied including xanthan gum, cellulosics such as hydroxyethylcellulose (HEC), carboxymethoxycellulose (CMC), lauryldimonium hydroxypropyl oxyethyl cellulose (Crodacel QL), hydroxypropylcellulose (HPC), and hydroxypropylmethylcellulose (HPMC), poly(acrylic acid), cyclodextrins, methyl acrylamido propyl triammonium chloride (MAPTAC), polyethylene oxide, polyvinylpyroliddone, polyvinyl alcohol, and propylene oxide/ethylene oxide random copolymers. Poloxamers may also be used as additives. Examples include both the Pluronic® polyols having an $(P_1)_a(P_2)_b(P_1)_a$ structure such as Pluronic® F38, L44, P65, F68, F88, L92, P103, P104, P105, F108, L122 and F127, as well as the reverse Pluronic® R series $(P_2)_a(P_1)_b(P_2)_a$ structure such as Pluronic® 17R2 and 25R8. Other miscellaneous materials include propyleneoxide, urea, triethanolamine, alkylphenol ethoxylates (Iconol series), and linear alcohol alkoxylates (Plurafac series).

Additives affect the viscosity of the compositions differently depending upon the nature of the additive and its concentration. Some additives will affect the initial or final viscosity, whereas others will affect the temperature range of the viscosity response, or both.

Potassium chloride and acetamide MEA are two examples of additives which decrease the final viscosity of the composition (see, Example 32). KCl (0.25%) added to a 1 wt% reversibly gelling polymer composition reduces the viscosity by about 3000 cps. See, Figure 7. The humectant, acetamide MEA, lowers the viscosity of a 1 wt% solution by approximately 1,500 cps (see, Figure 8).

Glycerin, ethanol and dimethicone copolymer have been shown to affect the temperature range over which the viscosity response occurs. Glycerin shifts the transition temperature to a slightly lower range from an initial 24-34 °C to about 24-30 °C, but does not affect the final viscosity (see, Example 28). The effect of ethanol on the viscosity is different at different concentration levels. At 5 wt% and 10 wt% added ethanol, the transition temperature is shifted to lower ranges, e.g., 24-29 °C and 20-29 °C, respectively. At 20 wt% added ethanol, the composition not only exhibits a lowering of the transition temperature, but also a marked increase in initial and final viscosity. See, Figure 9. Dimethicone copolymer (1 wt%) also changed the transition temperature, but in this instance the transition temperature range was raised to 28-41 °C. Thus, proper selection of additives permits the formulator to adjust the transition temperature to various ranges.

To further illustrate the scope of the changes that could be accomplished with additives, the effect of adding the surfactant Surfynol CT11 to the polymeric network is shown in Figure 10. In this example, the addition of 0.25% of the surfactant to a 1% polymer solution shifts the transition temperature downward.

These examples of the effects of formulation ingredients on the viscosity of the composition show that the polymeric network provides the formulator significant opportunities in creating compositions with different rheological properties by the judicious choice of additives. Significantly, the low temperature properties of the polymeric compositions are minimally affected by the additives while the properties of the gelled or viscosified form of the compositions can show dramatic effects.

The reversible viscosification of the polymer network at elevated temperatures makes the materials ideal for use as thickening agents in pharmaceutic and personal care products at any temperature above the transition. Another use of the "thickening" of solutions containing the polymer network as a thickener supplement in emulsions. Currently emulsifiers are often negatively effected by increased temperatures. An additive with reverse thermal viscosification properties, however, would react in exactly the opposite way, increasing its ability to emulsify as it gained three-dimensional structure upon heating above its transition temperature.

In the applications where the reversibly gelling polymer composition can act as a surfactant, the polymer network will have the ability to act as a primary emulsifier without any (or with very little) addition of traditional surfactant. The responsive polymer network will also act as a stabilizer for oil-soluble ingredients that would conventionally need to be solubilized by oils in formulation. The hydrophobic portion of the polymer network (PPO) forms domains which act as reservoirs for an oil-soluble or hydrophobic additive, such as a hydrophobic pharmaceutical agent, as is illustrated in Figure 11. The increase in viscosity above the transition temperature adds structure and yield value to the water phase and results in a highly stable emulsion for the hydrophobic additive.

The polymer network may be useful as a solubilization agent in pharmaceutic applications. A self-assembling system comprising the reversibly gelling polymer network exhibits thermogelation, pH sensitivity, and the ability to solubilize hydrophobic agents in aqueous media. When poloxamer is copolymerized with poly(acrylic acid) (PAA) according to the invention, the resulting copolymer network is bioadhesive and can be applied in a number of therapies. The materials described in this invention combine "reverse" thermoviscosification mucoadhesion, solubilization of hydrophobic and difficult to manage moieties, easy formulation, and protection of agents from degradation to provide a superior medium for pharmaceutic and personal care products.

In addition to the unique rheological properties provided by the polymeric network, the polymeric network is capable of solubilizing and releasing bioactive materials. Solubilization is expected to occur as a result of dissolution in the bulk aqueous phase or by incorporation of the solute in micelles created by the hydrophobic domains of the polymeric network. Release of the drug would occur through diffusion or network erosion mechanisms.

Those skilled in the art will appreciate that the polymer network compositions of the present invention may be utilized for a wide variety of pharmaceutic applications. To prepare a pharmaceutic composition, an effective amount of pharmaceutically active agent(s) which imparts the desirable pharmaceutic effect is

incorporated into the reversibly gelling polymer network composition of the present invention. Preferably the selected agent is water soluble, which will readily lend itself to a homogeneous dispersion through out the reversibly gelling polymer network composition; however, the polymer network has been demonstrated to significantly solubilize or suspend hydrophilic agents in order to improve formulation homogeneity (see, Example 34). It is also preferred that the agent(s) is nonreactive with the polymer network composition. For materials which are not water soluble, it is also within the scope of the invention to disperse or suspend lipophilic material throughout the polymer network composition.

A discussion of particular applications follows.

Esophageal and buccal applications. One indication for the use of this polymeric network would be as a coating to protect tissue from external or internal chemical challenges. For example, the polymeric network in the form of an esophageal formulation could coat the esophagus and protect it from the effects of acid, resulting from gastric reflux (GERD). Because of its ionic nature, the neutralized, polyacrylic acid component of the polymeric network could neutralize a certain amount of acid and prevent the acid from acting upon the tissue. In another variation, the polymeric network formulation could include acid absorbing substances, such as, aluminum oxide.

With the incorporation of bioactive materials, the polymeric network provides a suitable vehicle for delivering drugs within the esophageal lining. As explained above, its rheological and mucoadhesive properties are desirable attributes for controlling and facilitating drug delivery.

Opthalmic applications. Most ophthalmic drugs are applied to the eye topically to the precorneal area. The most common dosage form is a liquid drop. Drug bioavailability is generally low because liquid formulations are quickly cleared from the eye by tearing and blinking, resulting in the need for frequent dosing and uneven drug delivery.

The polymeric network provides a new vehicle for achieving greater bioavailability of topically administered ophthalmic drugs. Formulations containing it

can be applied as drops which viscosify or gel upon contact with eye. Since gelling can be accomplished with low concentrations of the polymer, blurring can be minimized upon drop instillation. Low solid concentrations also help to minimize crusting along the eyelid margins. See, Examples 35-37.

A particular advantage of the polymeric network is that, as a result of its rheological properties, compositions containing the polymer will evenly coat the precorneal surface. This is in contrast to other ophthalmic drug delivery vehicles which may gel upon application to the eye but which form deposits of the formulation that reside under one eyelid. The ability of the polymer to shear-thinning or to evenly spread over the precorneal surface is particularly advantageous in dry eye formulations or in the treatment of inflammation and wound healing conditions.

The use of the polymeric network would be indicated for delivering bioactive materials, such as, anesthetics, mydriatics and cycloplegics, antimicrobial agents (antibacterial, antifungal, antiviral), anti-inflammatory agents, agents for the treatment of glaucoma, ocular decongestants, diagnostic agents, and wound healing agents.

Nasal applications. The use of the polymeric network is also indicated for the delivery of drugs to the nasal cavity. Nasal drug delivery has been considered as an alternative to parenteral routes of administration of drugs that demonstrate low oral bioavailability. In order to increase the bioavailability of nasally administered drugs, efforts have been made to increase the residence time of formulations in the nasal cavity. Nasal delivery of drugs can offer advantages over other methods of delivery, including rapid systemic absorption, lower dosing, more rapid onset of desired therapeutic effects, and improved pharmacokinetics. In addition, it provides an alternative route for administering peptide drugs, which generally have low bioavailability via the oral route and are normally administered parenterally. See, Example 40.

The rheological properties of the polymeric network are uniquely suited to nasal delivery systems. Earlier results demonstrated that formulation variables can be manipulated to significantly affect the higher temperature viscosity of the polymeric network. These same variables have only minimal effects on the low temperature

viscosity. Therefore, formulations containing the polymeric network can be readily sprayed at low temperature; the subsequent viscosification occurs only after administration of the formulation and only at the site of application.

The polymeric network is also useful for delivering agents such as decongestants, antihistamines, anti-osteoporosis agents, hormones, antineoplastic agents, Parkinsonism drugs, etc.. The polymeric network is also indicated for the application of vaccines, such as those against the influenza virus.

A further desirable outcome of the use of the polymeric network in the delivery of nasal formulations is the prevention of roll back, or the loss of the formulation by rapid flow to the posterior section of the nasal cavity and into the esophagus. In addition to the negative effects on the delivery of the drug across the desired mucosal tissue, roll can lead to unpleasant taste sensations associated with some drug formulations. See, Example 41.

Veterinary applications. The reversibly gelling polymer network of the invention also may be useful in the treatment of not only human conditions but in providing treatments for animal care. For veterinary products, the polymeric network is indicated for the preparation of topical dermal products, such as antibacterials, antifungals, antipruritics, and antiseborrheia, antiodor, and antiseptic/wound healing preparations. Otic products would include ear cleaners with or without actives, such as, antifungals. Ophthalmic products would include eye moisturizers or antimicrobial preparations. The rheological, solubilizing, drug delivery, and chemical properties provide the formulator of veterinary products the latitude to prepare compositions in a variety of delivery forms and, more importantly, with regard to companion animals, with a non-oily quality.

Tablet Excipients. It has been demonstrated that the polymeric network of the invention can be processed by standard pharmaceutical processes, such as lyophilization and air drying. The reversible thermal viscosifying polymer network ma be reconstituted with water, phosphate buffer or calcium chloride solution, without loss or degradation of the rheological properties of the polymer. Thus, it is contemplated that the polymer network of the invention may also be incorporated as excipients into

tablets or granules for oral delivery. The polymer may be coated on an outer surface of the tablet or may be introduced in powder form into the tablet along with the active agent and other ingredients. The poloxamer:poly(acrylic acid) polymer network may be used to promote bioadhesion of the tablet and its contents with the mucosal lining of the gastro-intestinal tract to extend transit time.

Injectibles. The polymeric network of the invention is well-suited for use in injectable applications. A depot formulation may be prepared and administered at low viscosity to a subdermal or intramuscular site, for example. The polymer will viscosify and form a depot site, which will slowly release the active agent. The reversible thermally viscosifying polymer network, upon contact with body fluids including blood or the like, undergoes gradual release of the dispersed drug for a sustained or extended period (as compared to the release from an isotonic saline solution). This can result in prolonged delivery (over, say 1 to 2,000 hours, preferably 2 to 800 hours) of effective amounts (say, 0.0001 mg/kg/hour to 10 mg/kg/hour) of the drug. This dosage form can be administered as is necessary depending on the subject being treated, the severity of the affliction, the judgment of the prescribing physician, and the like.

Alternatively, the polymeric network may be prepared at higher viscosities in order to suspend microspheres or particles in the formulation. The formulation can then take advantage of the shear-thinning properties of the polymeric material. Thus, during injection, the formulation is subjected to shear stresses which reduce viscosity and allow an ordinarily viscous formulation to be introduced into the patient by injection. Cessation of the strain results in reestablishing the high viscosity of the formulation, so that the active agent may be slowly released therefrom.

The variety of different therapeutic agents which can be used in conjunction with the copolymers of the invention is vast. In general, therapeutic agents which may be administered via the pharmaceutical compositions of the invention include, without limitation: antiinfectives such as antibiotics and antiviral agents; analgesics and analgesic combinations; anorexics; antihelmintics; antiarthritics; antiasthmatic agents;

anticonvulsants; antidepressants; antidiuretic agents; antidiarrheals; antihistamines; antiinflammatory agents; antimigraine preparations; antinauseants; antineoplastics; antiparkinsonism drugs; antipruritics; antipsychotics; antipyretics, antispasmodics; anticholinergics; sympathomimetics; xanthine derivatives; cardiovascular preparations including calcium channel blockers and beta-blockers such as pindolol and antiarrhythmics; antihypertensives; diuretics; vasodilators including general coronary, peripheral and cerebral; central nervous system stimulants; cough and cold preparations, including decongestants; hormones such as estradiol and other steroids, including corticosteroids; hypnotics; immunosuppressives; muscle relaxants; parasympatholytics; psychostimulants; sedatives; and tranquilizers; and naturally derived or genetically engineered proteins, polysaccharides, glycoproteins, or lipoproteins. Suitable pharmaceuticals for parenteral administration are well known as is exemplified by the Handbook on Injectable Drugs, 6th edition, by Lawrence A. Trissel, American Society of Hospital Pharmacists, Bethesda, Md., 1990 (hereby incorporated by reference).

The polymeric network is effective in extending the duration of contact of preparations that have been applied to mucosal tissues. In providing a longer residence time, the polymeric network provides a valuable tool for increasing drug delivery across mucosal surfaces.

The polymeric network also may be used for products in which there is no bioactive ingredient. The function of the polymeric network would be to provide, for example, a protective or lubricating film to the surface of the tissue. For example, the polymeric network could be the basic ingredient for a lubricating drop for the eye. By its nature, that is, that of a hydrogel, it could provide a long lasting lubricious and moisturizing film to the eye of individuals suffering from dry eye conditions due to pathological states or environmental stress. Other similar indications would be for nasal or vaginal moisturizers.

It will also be appreciated that a sterile environment may be required. It is contemplated as within the scope of the invention that the reversibly gelling polymer

network compositions of the present invention may be prepared under sterile conditions. See, Example 16.

In the preparation of pharmaceutical compositions, problems can be encountered in the solubilization of hydrophobic bioactive materials. Because of its hydrophobic moieties the polymeric network is capable of facilitation such dissolution, even at the low concentrations which are used in formulating. To illustrate this property, the solubility of hydrophobic materials, such as, estradiol and progesterone in the polymeric network as a function of concentration of the polymeric system is shown in the following two examples. See, Example 34.

The solubility of the steroid hormones was measured by equilibration of excess hormone in aqueous solutions with and without the polymeric network, followed by centrifugation and filtration to remove the undissolved material. The concentrations of the hormones was determined spectrophotometrically at 240 nm (progesterone) or 280 nm (estradiol).

The solubility curves as a function of temperature for various concentrations of the polymeric network are shown in Figure 12A (estradiol) and Figure 13A (progesterone). The results show that increasing the concentration of the polymeric network increased the solubility of the hormones and that this solubility was greater at higher temperatures.

The kinetics of the in vitro release of the hormones from the polymeric network are shown in Figures 12B and 13B. These studies were performed using thermostatted, vertical Franz cells. Spunbonded poly(propylene) microfilters (15-20 micron retention) were used to separate the feed and receiving chambers. The receiving chamber consisted of 20% polyethylene glycol in water.

Figure 12B shows that the initial transport rate increases with decreasing concentrations of the polymeric network. Figure 13B shows that this initial transport rate also increases with a decrease in the temperature. Both of the these results are related to the changes in the macroviscosity of the compositions.

These in vitro studies have shown the advantage of the polymeric network in solubilizing and releasing hydrophobic bioactive materials. The usefulness of the

polymeric network, however, is not limited to hydrophobic bioactive materials. This property offers further advantages over other commonly used drug delivery vehicles. Dissolution of more hydrophilic materials is expected, as demonstrated in later examples, by a mechanism of dissolution in the bulk aqueous component of the formulations.

The poloxamer:poly(acrylic acid) polymer network has been evaluated under Good Laboratory Practice (GLP) standard protocols known in the art for toxicity in animal models and found to exhibit no toxic effects. The results of the toxicity study are summarized in the following Table 1. The non-toxicity of the polymer network makes it an ideal candidate for use in pharmaceutic compositions.

Table 1. Toxicity data for 6% poloxamer:poly(acrylic acid) solution at pH 7.

Reaction testes	mode of testing	results
Skin sensitization	guinea pig - topical	not a sensitizer
eye irritation	rabbit eye instillation	negative
primary dermal irritation	rabbit - topical	very slight edema (1 on a scale of 1-8)
acute dermal toxicity	rat - single dose (2g/kg)	no toxicity
acute oral toxicity	rat - single dose (5g/kg)	no toxicity
AMES test		negative

Preparation of pharmaceutic compositions may be accomplished with reference to any of the pharmaceutic formulation guidebooks and industry journals which are available in the pharmaceutic industry. These references supply standard formulations which may be modified by the addition or substitution of the reversible viscosifying polymer network of the present invention into the formulation. Suitable guidebooks include Pharmaceutics and Toiletries Magazine, Vol. 111 (March, 1996); Formulary: Ideas for Personal Care; Croda, Inc, Parsippany, NJ (1993); and Pharmaceuticon: Pharmaceutic Formulary, BASF, which are hereby incorporated in their entirety by reference.

The pharmaceutic composition may be in any form. Suitable forms will be dependant, in part, of the intended mode and location of application. Opthalmic and otic formulations are preferably administered in droplet or liquid form; nasal formulations are preferable administered in droplet or spray form, or may be administered as a powder (as a snuff); vaginal and rectal formulations are preferably administered in the form of a cream, jelly or thick liquid; veterinary formulations may be administered as a cream, lotion, spray or mousse (for application to fur or exterior surface); esophageal and buccal/oral cavity applications are preferably administered from solution or as a powder; film forming applications or dermal applications may be administered as a lotions, creams, sticks, roll-ons formulations or pad-applied formulations.

Exemplary drugs or therapeutics delivery systems which may be administered using the aqueous responsive polymer network compositions of the invention include, but are in no way limited to, mucosal therapies, such as esophageal, otic, rectal, buccal, oral, vaginal, and urological applications; topical therapies, such as wound care, skin care and teat dips; and intravenous/subcutaneous therapies, such as intramuscular, intrabone (e.g., joints), spinal and subcutaneous therapies, tissue supplementation, adhesion prevention and parenteral drug delivery. In addition, further applications include transdermal delivery and the formation of depots of drug following injection. It will be appreciated that the ionic nature of the "structural component" component of the responsive polymer network provides an adhesive interaction with mucosal tissue.

Because the reversibly gelling polymer network composition of the present invention is suited for application under a variety of physiological conditions, a wide variety of pharmaceutically active agents may be incorporated into and administered from the polymer network composition. The pharmaceutic agent that may be loaded into the polymer networks of the present invention are any substance having biological activity, including proteins, polypeptides, polynucleotides, nucleoproteins, polysaccharides, glycoproteins, lipoproteins, and synthetic and biologically engineered analogs thereof.

Examples of suitable pharmaceutic agents that might be utilized in a delivery application of the invention include literally any hydrophilic or hydrophobic biologically active compound. Preferably, though not necessarily, the drug is one that has already been deemed safe and effective for use by the appropriate governmental agency or body. For example, drugs for human use listed by the FDA under 21 C.F.R. 330.5, 331 through 361; 440-460; drugs for veterinary use listed by the FDA under 21 C.F.R. 500-582, incorporated herein by reference, are all considered acceptable for use in the present novel polymer networks.

Drugs that are not themselves liquid at body temperature can be incorporated into polymers, particularly gels. Moreover, peptides and proteins which may normally be lysed by tissue-activated enzymes such as peptidases, can be passively protected in gels as well. See, Gehrke et al. *Proceed. Intern. Symp. Control. Rel.* Bioact. Mater., 22:145 (1995).

Pharmaceutic agents includes pharmacologically active substances that produce a local or systemic effect in animals, plants, or viruses. The term thus means any substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease or in the enhancement of desirable physical or mental development and conditions in an animal, plant, or virus. The term "animal" used herein is taken to mean mammals, such as primates, including humans, sheep, horses, cattle, pigs, dogs, cats, rats, mice; birds; reptiles; fish; insects; arachnids; protists (e.g. protozoa); and prokaryotic bacteria. The term "plant" means higher plants (angiosperms, gymnosperms), fungi, and prokaryotic blue-green "algae" (i.e. cyanobacteria).

The pharmaceutically active compound may be any substance having biological activity, including proteins, polypeptides, polynucleotides, nucleoproteins, polysaccharides, glycoproteins, lipoproteins, and synthetic and biologically engineered analogs thereof. The term "protein" is art-recognized and for purposes of this invention also encompasses peptides. The proteins or peptides may be any biologically active protein or peptide, naturally occurring or synthetic.

Examples of proteins include antibodies, enzymes, steroids, growth hormone and growth hormone-releasing hormone, gonadotropin-releasing hormone, and its

agonist and antagonist analogues, somatostatin and its analogues, gonadotropins such as luteinizing hormone and follicle-stimulating hormone, peptide-T, thyrocalcitonin, parathyroid hormone, glucagon, vasopressin, oxytocin, angiotensin I and II, bradykinin, kallidin, adrenocorticotropic hormone, thyroid stimulating hormone, insulin, glucagon and the numerous analogues and congeners of the foregoing molecules. The pharmaceutical agents may be selected from insulin, antigens selected from the group consisting of MMR (mumps, measles and rubella) vaccine, typhoid vaccine, hepatitis A vaccine, hepatitis B vaccine, herpes simplex virus, bacterial toxoids, cholera toxin B-subunit, influenza vaccine virus, bordetela pertussis virus, vaccinia virus, adenovirus, canary pox, polio vaccine virus, plasmodium falciparum, bacillus calmette geurin (BCG), klebsiella pneumoniae, HIV envelop glycoproteins and cytokins and other agents selected from the group consisting of bovine somatropine (sometimes referred to as BST), estrogens, androgens, insulin growth factors (sometimes referred to as IGF), interleukin-I, interleukin-II and cytokins. Three such cytokins are interferon-.beta., interferon-.gamma. and tuftsin.

Examples of bacterial toxoids are tetanus, diphtheria, pseudomonas A, mycobacterium tuberculosis. Examples of HIV envelop glycoproteins are gp 120 and gp 160 for AIDS vaccines. Examples of anti-ulcer H.sub.2 receptor antagonists are ranitidine, cimetidine and famotidine, and other anti-ulcer drugs are omparazide, cesupride and misoprostol. An example of a hypoglycaemic agent is glizipide. Insulin is used for the control of diabetes.

Classes of pharmaceutically active compounds which can be loaded into a reversible thermal viscosifying polymer network composition include, but are not limited to, anti-AIDS substances, anti-cancer substances, antibiotics, immunosuppressants (e.g. cyclosporine) anti-viral substances, enzyme inhibitors, neurotoxins, opioids, hypnotics, antihistamines, lubricants tranquilizers, anti-convulsants, muscle relaxants and anti-Parkinson substances, anti-spasmodics and muscle contractants, miotics and anti-cholinergics, anti-glaucoma compounds, anti-parasite and/or anti-protozoal compounds, anti-hypertensives, analgesics, anti-pyretics and anti-inflammatory agents such as NSAIDs, local anesthetics, ophthalmics,

prostaglandins, anti-depressants, anti-psychotic substances, anti-emetics, imaging agents, specific targeting agents, neurotransmitters, proteins, cell response modifiers, and vaccines.

A more complete listing of classes of compounds suitable for loading into polymers using the present methods may be found in the *Pharmazeutische Wirkstoffe* (Von Kleemann et al. (eds) Stuttgart/New York, 1987, incorporated herein by reference). A more complete list of suitable pharmaceutic agents can be found in WO 97/00275, which is hereby incorporated by reference.

Exemplary pharmaceutical agents considered to be particularly suitable for incorporation into the pharmaceutical composition of the invention with retention of therapeutic effectiveness and other advantageous properties include but are not limited to imidizoles, such as miconazole, econazole, terconazole, saperconazole, itraconazole, metronidazole, fluconazole, ketoconazole, and clotrimazole, luteinizing-hormone-releasing hormone (LHRH) and its analogues, nonoxynol-9, a GnRH agonist or antagonist, natural or synthetic progestrin , such as selected progesterone, 17-hydroxyprogeterone derivatives such as medroxyprogesterone acetate, and 19-nortestosterone analogues such as norethindrone, natural or synthetic estrogens, conjugated estrogens, estradiol, estropipate, and ethinyl estradiol, bisphosphonates including etidronate, alendronate, tiludronate, resedronate, clodronate, and pamidronate, calcitonin, parathyroid hormones, carbonic anhydrase inhibitor such as felbamate and dorzolamide, a mast cell stabilizer such as xesterbergsterol-A, lodoxamine, and cromolyn, a prostaglandin inhibitor such as diclofenac and ketorolac, a steroid such as prednisolone, dexamethasone, fluromethylone, rimexolone, and lotepednol, an antihistamine such as antazoline, pheniramine, and histiminase, pilocarpine nitrate, a beta-blocker such as levobunolol and timolol maleate, a sunscreen agent, an acne medication such as salicylic acid, sulfur, resorcinol, resorcinol monoacetate, and benzoyl peroxide, an anti-dandruff medication such as coal tar, pyrithione zinc, salicylic acid, selenium sulfide, and sulfur, a dermatological agent such as bath oils, emollients, hydrating agents, astrigents, antipruritics, protectants, keratin-softening agents, and hydrocortisone, hydroquinone, or nicotine.

As will be understood by those skilled in the art, two or more pharmaceutical agents may be combined for specific effects. The necessary amounts of active ingredient can be determined by simple experimentation.

This material meets many of the requirements for an optimum transmucosal delivery system for proteins, including peptides. Effective and efficient delivery involves four primary elements: a method of holding an optimal quantity of peptides against the mucosa for an extended period; a method of controlling the release of the peptides in a desired pattern (e.g., burst, sustained, circadian, etc.), transferring the peptides from the mucosal surface to the blood sera or other target, and maintenance of activity of peptides. The measure of merit is the reliable achievement of a desired pharmaceutical effect with minimal wasted active material-for example, the achievement and sustaining of an effective level of active peptide in the blood stream for a given time period with minimal excess delivery and minimal loss of activity through inactivation or erosion.

The structural component and responsive component of the system can be chosen for protein delivery. The structural component can be a mucoadhesive material (acrylic acid). The structural component can be a material which erodes (acrylic acid) or one that degrades (hyaluronic acid). The backbone can be crosslinked, can involve comonomers, and can be of varying molecular weights or structures. These modifications to the backbone directly effect retention of the Peptide-gel system, patterns of release, and peptide activity.

In addition to the poloxamer:poly(acrylic acid) polymer network, additional pharmaceutically acceptable carriers may be included in the composition, such as by way of example only, emollients, surfactants, humectants, powders and other solvents.

Preservatives can be desirably incorporated into the pharmaceutic compositions of the invention to protect against the growth of potentially harmful microorganisms. Suitable preservatives include, but are not limited to, alkyl esters of para-hydroxybenzoic acid, hydantoin derivatives, parabens, propioniate salts, triclosan tricarbanilide, tea tree oil, alcohols, farnesol, farnesol acetate, hexachlorophene and quaternary ammonium salts, such as benzolconjure, and a variety of zinc and

aluminum salts. Pharmaceutic chemists are familiar with appropriate preservatives and may selects that which provides the required product stability. Preservatives are preferably employed in amounts ranging from about 0.0001% to 2% by weight of the composition.

Emollients can be desirably incorporated into the pharmaceutic compositions of the invention to provide lubricity to the formulation. Suitable emollients may be in the form of volatile and nonvolatile silicone oil, highly branched hydrocarbons and synthetic esters. Amounts of emollients may be in the range of about 0.1-30 wt%, and preferably about 1-20 wt%. A variety of oily emollients may be employed in the compositions of this invention. These emollients may be selected from one or more of the following classes: triglyceride esters; acetoglyceride esters; ethoxylated glycerides; alkyl esters of fatty acids having 10 to 20 carbon atoms; alkenyl esters of fatty acids having 10 to 20 carbon atoms; fatty acids having 10 to 20 carbon atoms; fatty alcohols having 10 to 20 carbon atoms; fatty alcohol ethers, such as ethoxylated fatty alcohols of 10 to 20 carbon atoms having attached thereto from 1 to 50 ethylene oxide groups or 1 to 50 propylene oxide groups; ether-esters such as fatty acid esters of ethoxylated fatty alcohols; lanolin and derivatives; polyhydric alcohol esters; wax esters; beeswax derivatives; vegetable waxes including carnauba and candelilla waxes; phospholipids; sterol including cholesterol and cholesterol fatty acid esters; and amides such as fatty acid amides, ethoxylated fatty acid amides, solid fatty acid alkanolamides.

Humectants may be added to the composition to increase the effectiveness of the emollient, to reduce scaling, to stimulate removal of built-up scale and improve skin feel. The amount of humectant may be in the range of about 0.5-30 wt% and preferably between 1-15 wt%.

By way of example only, in the case of antibiotics and antimicrobials may be included in the composition of the invention. Antimicrobial drugs preferred for inclusion in compositions of the present invention include salts of β-lactam drugs, quinolone drugs, ciprofloxacin, norfloxacin, tetracycline, erythromycin, amikacin, triclosan, doxycycline, capreomycin, chlorhexidine, chlortetracycline, oxytetracycline, clindamycin, ethambutol, hexamidine isethionate, metronidazole, pentamidine,

gentamicin, kanamycin, lincomycin, methacycline, methenamine, minocycline, neomycin, netilmicin, paromomycin, streptomycin, tobramycin, miconazole and amanfadine and the like.

A wide variety of acids, bases, buffers, and sequestrants can be utilized to adjust and/or maintain the pH and ionic strength of the compositions useful in the instant invention. Materials useful for adjusting and/or maintaining the pH and/or the ionic strength include sodium carbonate, sodium hydroxide, hydrochloric acid, phosphoric acid, sulfuric acid, acetic acid, sodium acetate, sodium hydrogen phosphate, sodium dihydrogen phosphate, citric acid, sodium citrate, sodium bicarbonate, triethanolamine, EDTA, disodium EDTA, tetrasodium EDTA, and the like.

A general method of making the responsive polymer:structural polymer network compositions of the present invention comprises solubilization of the responsive polymer, e.g., poloxamer, in a monomer of the structural polymer, e.g., acrylic acid monomer, followed by polymerization of the monomer. Polymerization may be accomplished by addition of a polymerization initiator or by irradiation techniques. The initiator may be a free radical initiator, such as chemical free radical initiators and uv or gamma radiation initiators. Conventional free radical initiators may be used according to the invention, including, but in no way limited to ammonium persulfate, benzoin ethyl ether, benzyl peroxide, 1,2'-azobis(2,4-dimethylpentanitrile) (Vazo 52) and azobisisobutyronitrile (AIBN). Initiation may also be accomplished using cationic or ionic initiators. Many variations of this methods will be apparent to one skilled in the art and are contemplated as within the scope of the invention. For example, the poloxamer component may be dissolved in an acrylic acid/water mixture instead of pure monomer. It may be desirable to remove unreacted monomer and/or free poloxamer from the resultant polymer network. This may be accomplished using conventional techniques, such as, by way of example, dialysis or sohxlet extraction.

Without intending to be bound by a particular mechanism or structure, the following scheme represents a possible chemical mechanism for the formation of the system here described. These mechanisms are presented by way of explanation and

are no way limiting of the invention. It is contemplated that these or other mechanistic routes may in fact occur in the formation of the polymer network of the present invention.

I. Initiation

RR --> 2R• (1)

R• + CH_2=CHCOOH ---> RCH_2CH•COOH (2)

II. Hydrogen Abstraction

R• + -OCHRCH_2O- ---> RH + -OCR•CH_2O- (3)

R• + -CH_2CH_2COOH ---> RH + -CH_2CH•COOH (4)

III. Chain Transfer

-CH_2CH•COOH + -OCH_2CRH- ---> -CH_2CH_2COOH + -OCH_2CR•- (5)

-OCH_2CR•O- + -CH_2CHCOOH ---> -OCH_2CRHO- + -CH_2CH•COOH (7)

IV. Propagation

RCH_2CH•COOH + CH_2=CHCOOH --> RCH_2CHCOOHCH_2CH•COOH (8)

V. Side Chain Branching Off AA Backbone

-CH_2CH•COOH- + CH_2=CHCOOH --> -CH_2CH(CH_2CH•COOH)COOH (9)

VI. AA Branching off Poloxamer Backbone

-OCH_2CR•O- + CH_2=CHCOOH --> -OCH_2CR(CH_2CH•COOH)O- (10)

VII. Homogenous Termination

2 -CH_2CH•COOH --> -CH_2CHCOOHCHCOOHCH_2- (11)

VIII. Heterogenous Termination with bonding of Pluronic to PAA

-CH_2CH•COOH + -OCH_2C•RO- --> -CH_2CH(-OCRCH_2O-)COOH (12a)

The scheme for bonding of poloxamer to acrylic acid may involve initiation (eq 1), hydrogen abstraction from the propylene or ethylene moiety of the poloxamer (eq 3), and attachment to acrylic acid via addition across the unsaturated bond (eq 10). Propagation (eq 8) leads to the final PAA.

Alternatively, the mechanism may proceed by initiation according to eqs. (1) and (2), propagation to form PAA (eq.8), a chain transfer reaction to generate a reactive poloxamer moiety (eq. 5), followed by addition of the reactive poloxamer

moiety to the unsaturated bond of acrylic acid (eq. 10) and subsequent propagation of the PAA chain.

Thus the polymer network may include a plurality of poly(acrylic acid)) units bonded to a single poloxamer unit or, alternatively, a plurality of poloxamer units bound to a single PAA backbone. Combinations of these alternatives are also a possibility.

Reverse phase polymerization may be used to prepare polymer network beads by dispersion of the poloxamer and acrylic acid monomer mixture in a nonpolar solvent such as hexane or heptane. The aggregating polymer/monomer solution is dispersed with agitation in the nonpolar solvent in order to suspend droplets of the solution. Polymerization of the monomer is initiated by conventional means (i.e., addition of a initiator or irradiation) in order to polymerize the monomer and form responsive polymer network beads. See, U.S.S.N. 08/276,532 filed July 18, 1995 and entitled "Useful Responsive Polymer Gel Beads" for further information on the preparation of polymer gel beads, herein incorporated by reference. Such a method may be particularly desirable to provide a heat sink for the heat generated in the exothermic polymerization reaction.

The polymer network complexes and aqueous gelling solutions of the present invention may be understood with reference to the following examples, which are provided for the purposes of illustration and which are in no way limiting of the invention.

Example 1 This example describes the synthesis of a polymer network and an aqueous responsive polymer network solution prepared using a triblock polymer of poly(ethyleneoxide) and poly(propyleneoxide), Pluronic® F27 polyol, and poly(acrylic acid). This example also characterizes the gelation and the physical properties of the resultant polymer network.

Synthesis. Block copolymer of poly(propyleneoxide) (PPO) and poly(ethyleneoxide) (PEO) having triad ABA structure $(PEO)_A(PPO)_B(PEO)_A$ (Pluronic® F127 NF polyol, Poloxamer 407 NF polyol, where "F" means Flakes, "12" means 12X300=3600 - MW of the PPO section of the block copolymer, "7" PEO in

the copolymer is 70 wt%, and nominal molecular weight is 12,600) from BASF (3.0 g) was dissolved in 3.0 g acrylic acid (Aldrich). This represents a substantially 1:1 weight ratio of Pluronic® F127 polyol and poly(acrylic acid). The solution was deaerated by N_2 bubbling for 0.5 h and following addition of 100 ml of freshly prepared saturated solution of ammonium persulfate (Kodak) in deionized water was kept at 70 °C for 16 h resulting in a transparent polymer.

Viscosity measurements. A known amount of the resultant polymer was suspended in 100 ml deionized water into which NaOH was added. Following swelling for 3 days while stirring, the pH of the resulting fine suspension was adjusted to 7. Samples of 15 ml each were taken, and pH in each vial was adjusted to desired value by addition of 1 M HCl or NaOH. Samples were then kept overnight and their viscosities were measured at different temperatures using Brookfield viscometer using either an SC4-18 or an SC4-25 spindle.

A control experiment was done with a physical blend of Pluronic® F127 polyol and poly(acrylic acid) (MW 450,000) available from Aldrich. Pluronic® F127 polyol and poly(acrylic acid) were dissolved together in deionized water at 1 wt% total polymer concentration and the resultant solution was adjusted to pH 7, stirred and kept in refrigerator. The responsiveness of the polymer network composition and the physical blend to temperature and pH is illustrated in Figures 2 and 6 which clearly demonstrate that the synthetic route outlined above resulted in a polymer network system that is sensitive to pH and temperature of the environment. Figure 14 is a viscosity vs. temperature graph comparing the gelling characteristics of the responsive polymer network composition (curve (a)) and the physical blend (curve (b)). The blend prepared by physically mixing of the triblock PEO/PPO/PEO polymer and poly(acrylic acid) did not exhibit viscosifying effect either as a function of temperature or pH.

It was generally observed that 0.5-5 wt% polymer network compositions made of Pluronic® F127 polyol and poly(acrylic acid) viscosify at temperatures of around 30 °C and higher if pH is adjusted to 6 or higher. The gelling effect was observed in polymer network compositions standing 3 months or longer. Repeated heating and

cooling of responsive polymer network compositions did not cause deterioration of the polymer network or the gelling effect. Solutions of either Pluronic® F127 polyol or poly(acrylic acid) (1-5 w% in water, adjusted to pH 6 or higher) or physical blends of the two lacked the reverse thermal gelling effects found for polymer network compositions.

Example 2. This example describes a standard operating procedure for the manufacture of the reversible gelling polymer network.

The procedure is based upon a 50 liter production. A NaOH solution was prepared by dissolving 131.8 g NaOH pellets in 131.8 mL DI water (50% solution). The NaOH was allowed to dissolve completely. The NaOH solution will be used to convert a percentage of the acrylic acid to sodium acrylate in situ. Acrylic acid monomer (4 kg) is charged into a monomer feed tank and agitated at 250 rpm. NaOH is added slowly. The precipitate formed as the acrylic acid is neutralized to sodium acrylate is allowed to dissolve. Pluronic® F127 (3.5 kg) is slowly added to the monomer feed tank. Pluronic® F127 is dissolved under continued agitation. Norpar 12 (a refined C-12 alkane) is added to the reaction vessel (37 L). The mixture is agitated at 100 rpm. Stabilizer solution of Ganex V-126 is prepared in 2L Norpar 12 and added to the reactor under agitation.

A reaction vessel was degassed using a nitrogen sparge introduced from the bottom of reactor and was continued throughout the reaction. Initiator (13.63 g Lauryl peroxide and 4.23 g Vazo 52 in 0.7 kg acrylic acid monomer) is introduced into the monomer solution. The monomer solution was transferred to the reaction vessel. Agitation was increased to 150 rpm. Nitrogen sparging continued for an additional 20 minutes and then heating began. Heating began at a rate of 0.5-1.0 °C/min up to 75 °C. The reaction began to exotherm at about 45-50 °C and is allowed to continue without cooling until a maximum is reached. It is then cooled to 75 °C using forced cooling. The reaction continued for 12 hours and was then cooled to 35 °C. The slurry was transferred into pails and the polymer beads were allowed to settle.

The slurry was filtered through Buchner Funnels with filter paper (11 μm pore size) until the bulk of the Norpar had been removed from the beads. The beads were

washed three times with heptane. The filtered beads were transferred to a Pyrex drying tray and spread on the tray in a uniform layer. The beads were dried under vacuum for 4 hours at 40-50 °C. The dried beads were analyzed as follows.

Elemental analysis. The elemental analysis was performed by Quantitative Technologies, Inc., Whitehouse, NJ using a Perkin Elmer 2400 CHN Elemental Analyzer. Analysis provided C (52.49%), H (7.50%), N (< 0.05%), the balance assumed to be oxygen (39.96%).

Thermal Gravimetric Analysis (TGA). The TGA method was performed by Massachusetts Material Research, Inc., West Boylston, MA using a Dupont TGA model 295. The assay was run using a temperature ramp from 30 to 500 °C/min. The resolution for the system was set to 4 (1.0 °C/min for all slope changes). The data was analyzed using the first derivative of the curve and using maxima and minima to mark transitions. The moisture content was also calculated in this manner. The first derivative yielded three maxima. The first transition (moisture) was 3.0% by weight, the second transition was 14.0% by weight and the third was 67.02% by weight. Residue (15.98% remained).

Molecular weight determination by gel permeation chromatography (GPC). The molecular weight was determined by GPC on a Hewlet Packard 1100 Liquid Chromatography system with a Viscotech T60 Triple Detector system. Three Waters Ultrahydrogel columns, 1000, 500 and 250 Å, were used for the separation. The mobile phase was 0.1M $NaNO_3$ and 0.01M K_2HPO_4 salt solution, pH adjusted with phosphoric acid to a pH of 8.0 ± 0.1. The flow rate for the separation was 0.9 mL/min. The column temperature was maintained at 15 °C. The injection volume for the assay was 50 µL. A PEO molecular weight standard of 23,000 Daltons was used to align the detectors. The result for the assay were:

M_n: 341,700 Daltons

M_p: 1,607,000 Daltons

M_w: 2,996,000 Daltons

Free poloxamer determination by GPC. The amount of free (unbound) poloxamer in the polymer matrix was determined using the above GPC method and

comparing the poloxamer peaks to that of a standard poloxamer solution. The typical result is approximately 18-22% free poloxamer by weight.

The effect of both the bonded and non-bonded poloxamer on the gelation properties of the responsive polymer network has been determined by extraction of the non-bonded poloxamer from the material. Such extraction studies have established that the graft co-polymer alone exhibits the characteristic reverse thermal gelation of the composition; however, the presence of non-bonded poloxamer component modulates the gelation process. The non-bonded poloxamer component can affect the temperature of transition (from liquid to gel) and the degree of transition and assists in a more controlled and reproducible transition.

Bound poloxamer determination by ethylene oxide (EO) titration. The EO titration was performed as follows. A 5 gm sample of the product polymer was extracted in dichloroethane for three hours at reflux temperatures. The solid is removed and dried under a vacuum for 12 hours at room temperature. The dry material is then analyzed using ASTM method D 2959-95, "Standard Test Method for Ethylene Oxide Content". The amount of EO in the sample is related to the amount of poloxamer bound to the polymer. The typical result is approximately 15 % by weight of EO.

The relative amount of free poloxamer may be varied dependent upon the relative proportions of starting materials and the method of polymerization. Although the residual solids presumably contain only poloxamer which is bonded to the poly(acrylic acid), i.e., a graft co-polymer, the material still shows strong viscosification when it is neutralized and dissolved in water. However, the temperature of viscosification is increased substantially and the degree of viscosification per gram of total solids is increased by removal of free poloxamer. Thus, the free poloxamer plays a role in modifying the extent and temperature of viscosification. The poloxamer undergoes conformational changes and changes to the critical micelle concentration as a function of temperature. The poloxamer will change from an open, non-aggregated form to a micellular, aggregated form with changes in temperature.

Residual acrylic monomer determination by gas chromatography (GC). The residual acrylic acid monomer was determined by GC analysis using a Hewlet Packard GC 5890A, using a HP-FFDAP-TPA 10 m x 0.53 mm x 1μm column. The sample was extracted and run in methanol. Using an internal standard ratio, the sample was compared to a one point calibration. The typical results for this assay were below 70 ppm acrylic acid monomer.

Residual Norpar solvent by GC. The residual Norpar in the sample was determined by GC using the above method and comparing the Norpar peaks to that of a standard. The typical results were below 1.5 wt%.

UV-vis spectrum. Optical clarity data of UV-vis spectrophotometer was obtained. A 1.0% solution in water was prepared and measured at 420 nm. Transmittance (%) was typically greater than 90%.

Differential scanning calorimetry (DSC). The DSC was performed by Massachusetts Material Research, Inc., West Boylston, MA using a temperature ramp from 30 to 350 °C at 5 °C/min. The resolution for the system was set to 4 (1.0°C/min for all slope changes). The assay yielded one endothermic event at 265 °C, typically 270 J/g.

Examples 3-9. This example describes the synthesis of a several reversible thermal gelling polymer network prepared using a variety of poloxamers and poly(acrylic acid). The gelation and the physical properties of the resultant polymer network compositions are reported in Table 2.

Table 2.

example	poloxamer	poloxamer composition	poloxamer: PAA	trans. temp.	comments
3	Pluronic® F88 Prill polyol	2400 MW PPO; 80 wt% PEO; nominal MW 11,400	1:1	48 °C	viscosity response curve shown in Figure 15
4	Pluronic® F127 NF polyol	3600 MW PPO; 70 wt% PEO; nominal MW 12,600	1:1	30 °C	pentaerythritol triallyl ether crosslink agent used
5	Pluronic® P104 polyol	3000 MW PPO; 40 wt% PEO; nominal MW 5,900	1:1	28 °C	viscosity response curve shown in Figure 16
6	Pluronic® P123 polyol	3600 MW PPO; 30 wt% PEO; nominal MW 5,750	1:1	25 °C	viscosity response curve shown in Figure 17
7	Pluronic® F127/Pluronic® F108 polyol blend (1:1)	as above	1:1.7	42 °C	polymer solid formed, dried; resolubilized in neutralizing solution
8	Pluronic® F88 polyol	as above	1:1.7	80 °C	polymer solid formed, dried; resolubilized in neutralizing solution
9	Pluronic® F127/Pluronic® F88 polyol blend (1:1)	as above	1:1.7	85 °C	polymer solid formed, dried; resolubilized in neutralizing solution

Example 10. This example describes the synthesis of a responsive polymer network gel composition prepared using Pluronic® F127 and a copolymer of methacrylic and acrylic acid.

Methacrylic acid (Aldrich, 0.2 g) and acrylic acid (Aldrich, 1.8 g) were mixed and used to dissolve 2.0 g Pluronic® F127. The solution was dearated for 0.5 h and, following addition of 100 :1 freshly prepared saturated solution of ammonium persulfate in deionized water, was kept at 70°C for 16 h resulting in a transparent

polymer. A sample of the polymer was suspended in deionized water with added NaOH. Following swelling for three day, pH was adjusted to 9.0. A 2 wt% composition viscosified at temperatures of 40°C and higher. Viscosity vs. temperature profile is shown in Figure 18.

Example 11. The following example demonstrates the effect of hydrophilic/hydrophobic ratio on the gelling temperature. Polymer network compositions were prepared from the following poloxamers shown in Table 3.

Table 3. Composition of poloxamers investigated.

triblock polyol polymer composition	MW of PPO block	wt% of PEO block
P103 $(PEO)_{37}(PPO)_{56}(PEO)_{37}$	3250	50
P104 $(PEO)_{25}(PPO)_{56}(PEO)_{25}$	3250	40
P105 $(PEO)_{16}(PPO)_{56}(PEO)_{16}$	3250	30

Table 3 shows that in this series, the fraction of PEO is reduced when the molecular weight of the PPO block is kept constant. Linse (*Macromol.* 26:4437-4449 (1993)) report phase diagrams for these copolymers in water were calculated and it was shown that two-phase boundaries corresponding to the beginning of aggregation are almost unaffected by the molecular mass, given a constant PEO/PPO ratio, whereas these boundaries shifted to lower temperature as the PEO content of the polymer is reduced at constant mass. The strong dependence of the PEO/PPO ratio is a consequence of the differing solubilities of PEO and PPO in water at the elevated temperatures. Thus one would suppose that aggregation that causes viscosification in the responsive polymer network composition should shift to lower temperature as PEO fraction decreases.

The poloxamer (3.0 g) was dissolved in 3.0 g acrylic acid. The solution was deacrated by N_2 bubbling for 20 min. and following addition of the 100 :1 of freshly

prepared saturated solution of ammonium persulfate in deionized water was kept at 70°C for 16 h resulting in a strong whitish polymer. A sample of the polymer obtained (0.4 g) was suspended in 40 ml deionized water into which NaOH was added. Suspended responsive polymer network particles were allowed to dissolve under constant stirring. The resulting 1 wt% polymer network solutions were subjected to the viscosity measurement at shear rate of 132 or 13.2 sec^{-1} using a SC4-18 spindle. It can be seen from Figure 19 that, firstly, viscosity of the 1 wt% responsive polymer network solutions before viscosification (at 20-24°C) decreases in the series $(PEO)_{37}(PPO)_{56}(PEO)_{37}$(F103) > $(PEO)_{25}(PPO)_{56}(PEO)_{25}$(F104) > $(PEO)_{16}(PPO)_{56}(PEO)_{16}$(F105) and, secondly, the temperature at which gelation shifts from about 45°C for $(PEO)_{37}(PPO)_{56}(PEO)_{37}$ to about 35°C for $(PEO)_{25}(PPO)_{56}(PEO)_{25}$ and $(PEO)_{16}(PPO)_{56}(PEO)_{16}$. Both results are in excellent agreement with the theory set forth in Linse.

Example 12. The aim of this example is three-fold: (i) to demonstrate responsive polymer network compositions using a responsive component other than triblock polyoxyalkylene copolymers, (ii) to preserve useful properties of responsive polymer network, namely, ease of synthesis, viscosifying at body temperature, bioadhesiveness, and entirely benign components, and (iii) to incorporate drug into the responsive polymer network composition. For these purposes, nonylphenyl ether of polyethyleneglycol (Nonoxynol 9, drug name is Igepal CO-630) was chosen. This remarkable compound is surface active, possesses cloud point at around 55 °C and is used as a spermicide and anti-HIV agent in vaginal applications. Synthesis and properties of the resulted responsive polymer network are described below.

Synthesis. Igepal® CO-630 (Rhone-Poulenc) (3.0 g) was dissolved in 3.0 g acrylic acid (Aldrich). The solution was deaerated by N_2 bubbling for 30 min and following addition of 100 Fl of freshly prepared 300 mg/ml solution of ammonium persulfate (Kodak) in deionized water was kept at 70 °C for 16 h resulting in a transparent solid polymer. A sample of the polymer obtained (2.0 g) was suspended in 100 ml deionized water into which 0.18 g NaOH was added. Suspended

responsive polymer network particles were allowed so swell for 1 day under constant stirring. The pH of the solution was adjusted to 7.0.

Viscosity measurement. Viscosity vs temperature effect for responsive polymer network made of Nonoxanol 9 and polyacrylic acid (1:1) in deionized water (pH 7) is presented in Figure 20. The viscosity is measured at shear rate of 2.64 sec-1 using a SC4-18 spindle which allows a very sensitive measurement. It can be seen that the responsive polymer network starts to viscosify at about 30°C and the viscosity approaches maximum at 55°C at which point aggregates are formed (cloudiness is developed) and the viscosity drops precipitously.

Example 13. The following example is related to release of an active agent from a poloxamer:poly(acrylic acid) polymer network. Drug loading and kinetics of release of the protein hemoglobin from poloxamer:poly(acrylic acid) polymer network is described.

Synthesis. Pluronic® F127 (3.0 g) was dissolved in 3.0 g acrylic acid. The solution was deaerated by N_2 bubbling for 0.5 h and following addition of 100 Fl of freshly prepared saturated solution of ammonium persulfate (Kodak) in deionized water was kept at 70°C for 16 h resulting in a transparent polymer. The resultant responsive polymer network obtained (5 g) was suspended in 95 ml deionized water into which NaOH was added. The resulting suspension was allowed to swell for 7 days.

Hemoglobin loading and release. A 5 wt% responsive polymer network composition (3 g) was allowed to swell for 16 h in 10 ml of 0.25 mg/ml solution of human hemoglobin (Sigma) in deionized water adjusted to pH 8. The resulting mixture was well shaken and placed into the feed chambers of customized vertical, static, Franz-like diffusion cells made of Teflon. The feed and receiver chambers of the diffusion cells were separated by mesh screens (# 2063). The receiver chamber was continuously stirred by a magnetic bar. The cells were allowed to equilibrate to either 25 or 37°C (in an oven). The feed and receiver phases consisted of 1 g of the hemoglobin-loaded responsive polymer network and 6 ml of phosphate-buffered saline (pH 7.4), respectively. In the control experiment, the feed phase was made of 1 g of

0.25 mg/ml hemoglobin solution. After the feed solution had been loaded into the cell, the kinetic time commenced. Samples of the receiver phase was withdrawn from time to time and their absorbance was measured spectrophotometrically at 400 nm. To calculate hemoglobin concentrations, corresponding calibration curves (absorbance in PBS versus hemoglobin concentration) were generated. The results of the kinetic experiment are presented in Figure 21. It can be seen that the rate of hemoglobin release from the polymer network was substantially lowered at 37°C when compared to that at 25°C, because of viscosity increase in the polymer network at elevated temperatures (see Figure 2). The protein released from the polymer network composition still retained its native structure, as was determined by comparison of uv-vis spectra of release hemoglobin and natural hemoglobin.

Example 14. The following example is related to release of an active agent from a poloxamer:poly(acrylic acid) polymer network. Drug loading and kinetics of release of the protein lysozyme from a polymer network is reported.

Lysozyme loading and release. A 5 wt% responsive polymer network composition (3 g) was allowed to swell for 16 h in 10 ml of 1 mg/ml solution of chicken egg-white lysozyme (Sigma) and 1.5 mg/ml sodium dodecyl sulfate (Aldrich) in deionized water adjusted to pH 8.5. The resulting mixture was well shaken and placed into the feed chambers of customized vertical, static, Franz-like diffusion cells made of Teflon. The feed and receiver chambers of the diffusion cells were separated by mesh screens (# 2063). The receiver chamber was continuously stirred by a magnetic bar. The cells were allowed to equilibrate to either 25 or 37°C (in an oven). The feed and receiver phases consisted of 1 g of the lysozyme-loaded responsive polymer network and 6 ml of phosphate-buffered saline (pH 7.4), respectively. In the control experiment, the feed phase was made of 1 g of 1 mg/ml lysozyme solution. After the feed solution had been loaded into the cell, the kinetic time commenced. Samples were withdrawn and their absorbance measured spectrophotometrically at 280 nm. A calibration curve was prepared for lysozyme concentration ranging from 0 mg/ml to 0.5 mg/ml in phosphate buffered saline. The results of the kinetic experiment are presented in Figure 22. It can be seen that the

rate of lysozyme release from the responsive polymer network composition was substantially lowered at 37°C when compared to that at 25°C, because of viscosity increase in responsive polymer network at elevated temperatures (see Figure 2).

In order to demonstrate the retention of the enzymatic activity of lysozyme, the lysozyme released from the responsive polymer network composition was assayed using Micrococcus lysodeikticus cells and compared to that of original lysozyme. The enzymatic activity of lysozyme was the same, within the error of the assay (15%), as that of the original lysozyme. Control without lysozyme in presence of sodium dodecyl sulfate did not show any appreciable lysis of the cells.

Example 15. The following example is related to release of an active agent from a poloxamer:poly(acrylic acid) polymer network. Drug loading and kinetics of release of insulin from a responsive polymer network composition is reported.

Insulin loading and release. A 5 wt% responsive polymer network composition (3 g) was allowed to swell for 16 h in 10 ml of 5 mg/ml solution of bovine Zn^{2+}-insulin (Sigma) in deionized water adjusted to pH 7. The resulting mixture was well shaken and placed into the feed chambers of customized vertical, static, Franz-like diffusion cells made of Teflon. The feed and receiver chambers of the diffusion cells were separated by mesh screens (# 2063). The receiver chamber was continuously stirred by a magnetic bar. The cells were allowed to equilibrate to either 25 or 37°C (in an oven). The feed and receiver phases consisted of 1 g of the insulin-loaded responsive polymer network and 6 ml of phosphate-buffered saline (pH 7.4), respectively. In the control experiment, the feed phase was made of 1 g of 5 mg/ml insulin solution. After the feed solution had been loaded into the cell, the timing commenced. Samples were withdrawn and their absorbance was measured spectrophotometrically at 280 nm. A calibration curve was prepared for insulin concentration ranging from 0 mg/ml to 1.25 mg/ml in phosphate buffered saline. The results of the kinetic experiment are presented in Figure 23. The rate of insulin release from responsive polymer network was substantially lowered at 37°C when compared to that at 25°C, because of viscosity increase in responsive polymer network at elevated temperatures (see Figure 2).

Example 16. This example demonstrates the preparation of a sterile reversibly gelling polymer network aqueous composition and the stability of the composition to sterilization. The polymer network is prepared as described in Example 1, except that the composition is prepared at 2 wt% Pluronic® F127 polyol/poly(acrylic acid). After dissolution of the 2 wt% polymer network in water, the viscosity is measured. The composition then is sterilized by autoclaving at 121°C, 16 psi for 30 minutes. Viscosity is determined after sterilization. The corresponding curves for viscosity (a) before and (b) after sterilization are shown in Figure 24 and establish that minimal change in the viscosity profile of the material has occurred with sterilization.

Examples 17-32. These examples show additives which may be used to affect the transition temperature overall viscosification of the polymer network composition.

A 1 wt% polymer network was prepared in deionized water at pH 7 in which a variety of additives were included in the composition. The effect of the additive was determined by generation of a Brookfield viscosification curve. Results are reported in Table 4.

Table 4.

Example No.	Additive (wt%)	Effect of additive on:	
		transition temp. (°C)	final viscosity (% change)
17	1,2-methyl pyrrolidone (5)	I (1.8)	N
18	Rhodapex CO-436 (2)	I (1.6)	N
19	Dow Corning 190 (2)	I (5)	I (150)
20	isopropyl alcohol (0.5)	I (3.1)	I (45)
21	Pluronic® L122 (1)	D (4.4)	D (13)
22	Pluronic® F88 (1)	N	I (41)
23	Tween 80 (0.5)	N	I (18)
24	Germaben© II (1)	D (9)	I (100)
25	Iconol NP-6 (1)	D (9)	I (500)
26	Plurafac C-17 (0.5)	I (5.2)	D (36)
27	Dow Corning 193 (0.75)	I (4.1)	D (12)
28	glycerin (5)	D (2)	N
29	UC 50-HB-170/EO/PO random copolymer (0.5)	N	N
30	PVP K15 (1)	N	N
31	MAPTAC (1)	N	D (8)
32	potassium chloride (0.25)	N	D (34)

I = increase; D = decrease; and N = no change

Example 33. This example demonstrates the preparation of pharmaceutic compositions of formulations tailored to particular applications.

(a) Formulations including a nonionic surfactant formulation: An O/W (oil-in-water) emulsion was made by combining the following ingredients utilizing conventional mixing techniques:

Table 5.

Ingredient	% w/w
10 % wt. 1:1 responsive polymer network as prepared in Example 1	20.0
Emulsifying Wax NF[1]	2.5
Mineral Oil	5.0

[1] Polowax available from Croda

Into a vessel equipped with a high efficiency homogenizer, the formula amount of all ingredients is added, water is added to 100% w/w and allowed to mix to homogeneity. This formulation contains a nonionic surfactant and gives an emulsion that is fluid at room temperature but viscosifies above 32°C.

(b) Formulations including a cationic surfactant formulation: An O/W (oil-in-water) emulsion was made by combining the following ingredients utilizing conventional mixing techniques:

Table 6.

Ingredient	% w/w
10 % wt. 1:1 responsive polymer network as prepared in Example 1	20.0
Behentrimonium Methosulfate (and) Cetearyl alcohol[1]	2.5
Mineral Oil	5.0

[1] Incroquat Behenyl TMS available from Croda

Into a vessel equipped with a high efficiency homogenizer, the formula amount of all ingredients is added and allowed to mix to homogeneity. This formulation

contains a cationic surfactant and gives an emulsion that is fluid at room temperature but viscosifies above 32°C.

(c) Formulations including an anionic surfactant formulation: An O/W (oil-in-water) emulsion was made by combining the following ingredients utilizing conventional mixing techniques:

Table 7.

Ingredient	% w/w
10 % wt. 1:1 responsive polymer network as prepared in Example 1	20.0
Cetearyl Phosphate (and) Cetearyl alcohol[1]	2.5
Mineral Oil	5.0

[1] Crodafos CES available from Croda

Into a vessel equipped with a high efficiency homogenizer, the formula amount of all ingredients is added, water is added to 100% w/w and allowed to mix to homogeneity. This formulation contains a anionic surfactant and gives an emulsion that is fluid at room temperature but viscosifies above 32°C.

(d) Vaginal Moisturizer: An oil-free, lubricous, vaginal moisturizer is made by combining the following ingredients utilizing conventional mixing techniques:

Table 8.

Ingredient	% w/w
10 % wt. 1:1 responsive polymer network as prepared in Example 1	20.0
Glycerin USP	5.0
PPG-2 Myristyl Ether Propionate[1]	3.0
DL-Panthenol	0.5
Germaben® II[2]	0.1
Disodium EDTA	0.2
Citric Acid	0.01
USP Purified Water	71.19

[1] Crodamol PMP available from Croda

[2] Germaben® II available from Sutton Laboratories

To one vessel, equipped with a Lightnin' Mixer with a 3 blade paddle prop, the full amount of USP Purified Water is added. The water is then heated to 80°C and held for 20 minutes. The water is then cooled to 50°C , while maintaining the temperature, with moderate to vigorous mixing, the formula amount of Disodium EDTA, Citric Acid, DL-Panthenol, Glycerin, PPG-2 Myristyl Ether Propionate, and Germaben® II is added. These materials are allowed to dissolve at 50°C. After dissolution, the vessel is then cooled to 20°C. To another vessel, equipped with a high efficiency homogenizer, the formula amount of responsive polymer network is added. The responsive polymer network vessel is then cooled to 4°C. After cooling, while vigorously homogenizing, the contents of the first vessel is added to the second vessel, and allowed to mix to homogeneity.

The composition displays a flowable creamy lotion appearance with excellent moisturizing, emolliency, spreadability and absorption characteristics at room temperature, and after heating the formulation to 32°C, the composition thickens to a gel-like consistency.

(e) Formulation for Management of Bacterial Vaginosis: An oil-free, lubricous, bacterial vaginosis treatment is made by combining the following ingredients utilizing conventional mixing techniques:

Table 9.

Ingredient	% w/w
10 % wt. 1:1 responsive polymer network prepared as in Example 1	20.0
Glycerin USP	5.0
Metronidazole	0.75
DL-Panthenol	0.5
Germaben® II[1]	0.1
Disodium EDTA	0.2
Citric Acid	0.01
USP Purified Water	73.44

[1] Germaben®II available from Sutton Laboratories

To one vessel, equipped with a Lightnin' Mixer with a 3 blade paddle prop, the full amount of USP Purified Water is added. The water is then heated to 80°C and held for 20 minutes. The water is then cooled to 50°C , while maintaining the temperature, with moderate to vigorous mixing, the formula amount of Disodium EDTA, Citric Acid, DL-Panthenol, Glycerin, Metronidazole, and Germaben®II is added. These materials are allowed to dissolve at 50°C. After dissolution, the vessel is then cooled to 20°C. To another vessel, equipped with a high efficiency homogenizer, the formula amount of responsive polymer network is added. The responsive polymer network vessel is then cooled to 4°C. After cooling, while vigorously homogenizing, the contents of the first vessel is added to the second vessel, and allowed to mix to homogeneity.

The composition displays a flowable jelly appearance with excellent spreadability and absorption characteristics at room temperature, and after heating the formulation to 32°C, the composition thickens to a gel-like consistency.

(D) Formulation for Management of Bacterial Candidiasis: An Oil Free, lubricous, bacterial candidiasis treatment is made by combining the following ingredients utilizing conventional mixing techniques:

Table 10.

Ingredient	% w/w
10 % wt. 1:1 responsive polymer network prepared as in Example 1	20.0
Glycerin USP	5.0
Miconazole Nitrate	2.0
DL-Panthenol	0.5
Germaben® II[1]	0.1
Disodium EDTA	0.2
Citric Acid	0.01
USP Purified Water	72.19

[1] Germaben® II available from Sutton Laboratories

To one vessel, equipped with a Lightnin' Mixer with a 3 blade paddle prop, the full amount of USP Purified Water is added. The water is then heated to 80°C

and held for 20 minutes. The water is then cooled to 50°C , while maintaining the temperature, with moderate to vigorous mixing, the formula amount of Disodium EDTA, Citric Acid, DL-Panthenol, Glycerin, Miconazole Nitrate, and Germaben® II is added. These materials are allowed to dissolve at 50°C. After dissolution, the vessel is then cooled to 20°C. To another vessel, equipped with a high efficiency homogenizer, the formula amount of responsive polymer network is added. The responsive polymer network vessel is then cooled to 4°C. After cooling, while vigorously homogenizing, the contents of the first vessel is added to the second vessel, and allowed to mix to homogeneity.

The composition displays a flowable jelly appearance with excellent spreadability and absorption characteristics at room temperature, and after heating the formulation to 32°C, the composition thickens to a gel-like consistency.

(g) Topical Hormone Delivery Formulation: An oil-free, spreadable, topical hormone treatment using estradiol as the hormone is made by combining the following ingredients utilizing conventional mixing techniques:

Table 11.

Ingredient	% w/w
10 % wt. 1:1 responsive polymer network prepared as in Example 1	20.0
Glycerin USP	5.0
Estradiol	0.1
DL-Panthenol	0.5
Germaben® II[1]	0.1
Disodium EDTA	0.2
USP Purified Water	74.1

[1] Germaben® II available from Sutton Laboratories

To one vessel, equipped with a Lightnin' Mixer with a 3 blade paddle prop, the full amount of USP Purified Water is added. The water is then heated to 80°C and held for 20 minutes. The water is then cooled to 50°C , while maintaining the temperature, with moderate to vigorous mixing, the formula amount of Disodium EDTA, DL-Panthenol, Glycerin, Estradiol and Germaben® II is added. These materials are allowed to dissolve at 50°C. After dissolution, the vessel is then cooled

to 20°C. To another vessel, equipped with a high efficiency homogenizer, the formula amount of responsive polymer network is added. The responsive polymer network vessel is then cooled to 4°C. After cooling, while vigorously homogenizing, the contents of the first vessel is added to the second vessel, and allowed to mix to homogeneity.

The composition displays a flowable jelly appearance with excellent spreadability and absorption characteristics at room temperature, and after heating the formulation to 32°C, the composition thickens to a gel-like consistency.

(h) Nasal Decongestant Formulation: A non-drip nasal decongestant was made by combining the following ingredients utilizing conventional mixing techniques:

Table 12.

Ingredient	% w/w
5% wt. 1:1 responsive polymer network as prepared in Example 1	12.0
Polyvinyl Alcohol (78-82% Hydrolyzed)[1]	2.5
Triblock poloyol polymers	0.2
Oxymetazoline Hydrochloride	0.05
Benzalkonium Chloride	0.015
USP Purified Water	85.435

[1]Airvol 603 is available from Air Products

To one vessel, equipped with a Caframo mixer with a three blade paddle prop, the full amount of USP purified water was added. With moderate to vigorous mixing the formula amount of Airvol 603, Oxymetazoline Hydrochloride, and Benzalkonium Chloride was added. This material was allowed to mix until dissolved. The formula amount of responsive polymer was then added with moderate to vigorous mixing.

(i) Opthalmic Formulation: A bioadhesive eye drop formulation is made by combining the following ingredients utilizing conventional mixing techniques:

Table 13.

Ingredient	% Weight
USP Purified Water	91.02
Polaxamer	2.5
Mannitol	2.0
active ingredient	1.5

responsive polymer composition	1.2
Polyvinyl Alcohol (78-82% Hydrolyzed)[1]	0.5
Benzalkonium Chloride	0.01
Sodium Citrate	0.45
5N Sodium Hydroxide	0.82

[1]Airvol 603 is available from Air Products.

To one vessel, equipped with a Caframo mixer with a three blade paddle prop, the full amount of USP purified water was added. With moderate to vigorous mixing, the formula amount of Airvol 603, mannitol, active, and Benzalkonium Chloride was added. This material was allowed to mix until dissolved. The formula amount of sodium citrate was then added and allowed to dissolve. This was followed by the addition of the formula amount of Pluronic® F127. This was then allowed to dissolve and the formula amount of responsive polymer composition was then added with moderate to vigorous mixing.

(j) Otic Formulation:

Table 14.

Ingredient	% w/w
5% wt. 1:1 responsive polymer network as prepared in Example 1	10.0
USP Purified Water	90.0
active	0.1-1.0

To one vessel, equipped with a Caframo mixer with a three blade paddle prop, the full amount of USP purified water is added. With moderate to vigorous mixing the formula amount of active is added. This material is allowed to mix until well dispersed. The formula amount of responsive polymer network is then added with moderate to vigorous mixing.

(k) Veterinary Spray Formulation:

Table 15.

Ingredient	% w/w
5% wt. 1:1 responsive polymer network as prepared in Example 1	20.0
USP Purified Water	90.0
glycerin	5.0
Hydrocortisone	0.5

Example 34. Solubilization studies of model hydrophobic pharmaceutical agents in the poloxamer: poly(acrylic acid) polymer network: estradiol and progesterone. This example is presented to demonstrate the solubilization and delivery of a hydrophobic bioactive material in the polymeric network. Progesterone and estradiol were used as the hydrophobic agents.

Acrylic acid (99%), fluorescein (98%), β-estradiol (98%), and progesterone (98%) were all obtained from Aldrich and used as received. Pluronic® F-127 NF was obtained from BASF. Poly(oxyethylene-b-oxypropylene-b-oxyethylene)-g-poly(acrylic acid) copolymers (responsive polymer network) were synthesized by free-radical polymerization of acrylic acid in the presence of poloxamer as described above. The polymer network copolymers discussed here were composed of about 1:1 ratio of PAA to poloxamer. The rheological properties of polymer network were assessed using LVDV-II+ and RVDV-II+ Brookfield viscometers. The microscopic light scattering of 21 nm poly(styrene) latex particles in deionized water and 1 w% reversibly gelling polymer network was measured using He-Ne laser as described previously (See, Matsuo, E.S., Orkisz, M., Sun, S.-T., Li, Y., Tanaka, T., Macromolecules, 1994, 27, 6791). The solubility of fluorescein and hormones in aqueous solutions was measured by the equilibration of excess solubilizate with the corresponding solution following removal of undissolved species by centrifugation and filtration. Hydrophobic agents were assayed spectrophotometrically at 240 (progesterone) or 280 nm (estradiol), or by using 70/30 w/w H_2SO_4/MeOH (Tsilifonis-Chafetz reagent). In vitro hormone release studies were conducted using

thermostatted, vertical Franz cells. Spunbonded polypropylene microfilters (micron retention, 15-20) were used as a membrane separating feed and receiver phases in Franz cells. The responsive polymer network, water, ethanol, and 20% PEG in water were observed to wet the membrane. The receiver solutions consisted of 20 w% PEG in water (pH 7) and were stirred by magnetic bars. The feed phases composed of responsive polymer network were loaded with either estradiol or progesterone. Each hormone was dissolved in ethanol and the resulting solution was added into the responsive polymer network.

Equilibrium solubility vs. temperature plots for estradiol and progesterone (partition coefficient octanol/water (P) 7200 and 5888, respectively, in aqueous solutions of Pluronic® F127 polyol and responsive polymer network are presented in Figures 12 and 13. It can be seen that increasing temperature and concentration (C) of polymers in the solution raises the amount of the hormone dissolved. In Figure 12A, vertical lines represent critical micellar temperatures (CMT) for corresponding Pluronic F127 polyol solutions. It is interesting to note that the slope of the solubility-temperature plots increased as temperature reached CMT, indicating that solubilization in the Pluronic solutions was predominantly due to the formation of micelles. Similar trend was observed in the reversibly gelling polymer network solutions. The S values in 5% aqueous solutions of branched PAA did not exceed 15 and 40 μg/mL at 60 °C for estradiol and progesterone, respectively. The solubility values found for reversibly gelling polymer network were the same as S in parent Pluronic solutions of equivalent concentrations. Therefore, it may be suggested that solubilization behaviors of the reversibly gelling polymer network are governed by the properties of the poloxamer incorporated into it. A detailed analysis of thermodynamic data may be found in co-pending application U.S.S.N. 60/034,805, filed January 2, 1997, which is hereby incorporated by reference.

Solubilization was found to be spontaneous at all temperatures, and the solubilization was endothermic, similar to the solubilization of estriol, as well as indomethacin, by the poloxamer. Notably, ΔS of solubilization was always positive, suggesting that the more ordered water molecules surrounding hydrophobic estradiol

molecules moved to the less ordered bulk phase when the estradiol was transferred to the hydrophobic core of PPO segments in responsive polymer network. The aggregation of the PPO segments at elevated temperatures provides not only temporary cross-linking in the gel, but also a thermodynamically "friendly" environment for the hydrophobic drugs. A similar trend is indicated by the lowering the onset of gelation of the responsive polymer network upon solubilization of fluorescein (Log P 2.1) (Figure 25).

In vitro study of hormone release from responsive polymer network shows an increase in the initial transport rate with either decreasing total polymer concentration in the formulation or decreasing temperature (Figures 12 B and 13B). These effects are related to the changes in macroscopic viscosity of the responsive polymer network, which erodes more rapidly from the feed phase through the membrane into the receiver compartment as the viscosity decreases (Figure 26). The degree of the responsive polymer network erosion was measured by weighing hormone-loaded responsive polymer network before and after kinetic experiment.

Figure 27 shows that the relative amount of progesterone penetrating into the receiver phase decreased 4-fold with the increase of total polymer concentration (bar graph A), whereas the total relative amount of progesterone stayed almost constant as total polymer concentration in the responsive polymer network increased (bar graph B). This result shows the existence of two routes of transport of hydrophobic drugs in our model system. Firstly, the drug incorporated into aggregates within the reversibly polymer network system can flow through the membrane along with the erosion of the polymer network; secondly, the drug not associated with the reversibly gelling polymer network aggregates can diffuse out of the polymer network in the feed phase. The second process should not be related to the viscosity of the reversibly gelling polymer network.

Example 35. This example demonstrates delivery the ability of a poloxamer:poly(acrylic acid) polymeric network in retaining a liquid formulation in the precorneal area of the eye.

The delivery of drug across the tissues of the front surface of the eye is hindered by the protective mechanisms of tearing, eyelid blinking, and the epithelial barrier. Normal aqueous compositions that are applied to the high are cleared within minutes. The following example illustrates the retention time of pharmaceutical agents applied to the eye using the pharmaceutical composition of the invention.

A 50 μL drop of a 0.0001% fluorescein solution in 1% of an aqueous polymeric network was applied to the eye of two rabbits. The clearance of the formulation from the eye was followed by slit-lamp fluorophotometry. A buffered solution of fluorescein was used as the control. The fluorescence measurements as a function of time, post instillation, are shown in Figure 28.

The results show that for the buffered solution (curve 290 in Figure 28) the clearance half time was less than ten minutes, while that for the polymeric network composition (curve 292 in Figure 28) was approaching 80 minutes. Thus, the polymeric network significantly prolonged the fluorescein residence time in the precorneal area.

Example 36. This experiment reports the result of gamma scintigraphy employed as a non-invasive means of monitoring the residence time of the opthalmic compositions of the invention in the rabbit cornea.

A two-way cross over study was carried out on six New Zealand White rabbits comparing a poloxamer:poly(acrylic acid) polymer network with a control saline solution. The hydrogel formulation was radiolabelled by the inclusion of 25 μl ^{99m}Tc-DTPA to give an activity of 3MBq per dose (20 μl). The saline solution was similarly labeled. The dose was delivered directly onto the cornea using a positive displacement pipette and the animal was immediately positioned for imaging. Scintigraphic imaging was carried out using an IGE maxicamera II with a pin-hole collimator. Imaging for the hydrogel included a dynamic acquisition for 15 minutes (60 frames at 10sec/frame and 10 frames at 30 sec/frame) followed by two static images at 30 and 60 minutes. The saline was imaged dynamically for only 10 minutes (60 frames at 10sec/frame).

Gelation of the hydrogel on the corneal surface occurred immediately and could be visually observed. Dramatically increased retention time was observed with the poloxamer:poly(acrylic acid) polymer composition between the two formulations, as is illustrated in Figure 29. Saline clearance half-time was 45 seconds, as compared to 1150 seconds for the poloxamer:poly(acrylic acid) polymer composition. Figure 29 includes comparison of clearance half-times for other commercially available materials, which have been evaluated using the identical technique (J.L. Greaves et al., *Current I. Res* 9(5):415 (1990)). The ophthalmic formulation of the invention exhibited comparable performance to GelRite ® in humans and was far superior to all other materials compared. GelRite® is a trademark for a polysaccharide available from Merck; HEC is hydroxyethylcellulose; and Carbopol® is a polyacrylic acid available from BF Goodrich.

Example 37. The following example reports on the results on the bioavailability of the mydriatic drug, tropicamide, in the eye.

A 0.1% solution of tropicamide was prepared in a 0.1% solution of the polymeric network; a similar concentration of the drug in saline was used as the control. Fifty microliters of each solution was applied to the precorneal area a rabbit. The pupillary diameter change was measured with a micrometer at predetermined intervals post-instillation.

The calculated parameters of the response are presented in Table 16. These results indicate that the polymeric network formulation of tropicamide increased the area under the curve for the mydriatic response as compared to saline. It also prolonged the duration and increased in the intensity of the response.

Table 16.

0.1% tropicamide solution in stated carrier	AUC (relative to saline)	I_{max} (mm)	T_{max} (min)	duration
0.1% solution of the polymeric network	2.8	3.04	2.0	24
various commerically used polymeric vehicles[1,2]	1.4-1.7	2.1-2.5	0.6-1	10.5-12.3
saline	1.0	2.63	0.5	10

[1] using a 0.2% tropicamide solution; low MW hydroxypropylcellulose (4.5%); medium MW hydroxypropylcellulose (1.4%); carboxymethyl cellulose (1.63%); PVA (5.0%); PVP (7.5%).

[2] *Inter. J. Pharm.*, 20:187 (1984).

These results indicate that the polymeric network is useful in delivering drugs to the eye by topically administering a formulation of the drug with the polymeric network to the precorneal area. It demonstrates significant improved performance over control saline solution and also other commerically available polymeric vehicles.

Example 38. In the following example, the clearance of the reversibly gelling polymeric network from the nasal cavity has been monitored using gamma scintigraphy, as described in Example 36.

A 5 mL sample of the formulation shown in Table 17 was mixed with 3mbq 99m-Tc-DTPA and mixed thoroughly. The formulation was loaded into a spray device for nasal administration of ca. 200 μL doses to each individual. The study was performed on two healthy males on two occasions. The radiolabeled formulation was administered to one nostril of each subject using the spray device. Scintigraphy images of thirty second duration were taken periodically following administration of the formulation. The polymeric formulation was deposited anteriorly in each subject. The averaged data that was corrected for background and isotope decay is presented in Figure 30.

Table 17.

Ingredient	% weight	amount (g)
USP purified water	96.74	29.10
Polyvinyl alcohol; 78-82% hydrolyzed (Airvol 603)	1.25	0.625
reversibly gelling polymer network	0.8	20.0 g of a 2.0 wt% solution
poloxamer (Pluronic F127)	0.4	0.2
5N NaOH	0.8	Added in 2 wt% reversibly gelling polymer network
benzalkonium chloride	0.015	0.074 g of a 16 wt% soln.

The experiment demonstrated that the polymeric formulation experienced a two phase clearance from the nasal cavity. The half time clearance was approximately 1.5 hours, and at least 15% of the administered dose was retained in the nasal cavity for at least 17 hours. The formulation was cleared via the esophageal and gastrointestinal tract and it did not prove irritating to the nose.

The nasal formulation of the invention exhibited a $t_{1/2}$ of 96 minutes, which compares favorably with conventional polymeric vehicles such as methylcellulose (40-70 minutes; *J. Pharm. Sci.* 77(5):405 (1988)) and hydroxypropylcellulose (60-140 minutes; *Inter. J. Pharm.* 43:221 (1988)). However, the cellulose-based vehicles exhibited a considerably higher initial viscosity, making them unsuitable for spray application. In contrast, the poloxamer:poly(acrylic acid) polymeric vehicle, while demonstrating sufficient viscosity and bioadhesiveness after application, was of low initial viscosity and could be easily applied by spray.

Example 39. In the following example, the clearance of the reversibly gelling polymeric network from the nasal cavity has been monitored using fluorescein retention.

A 3.3 μL dose of a 0.3% fluorescein solution in a 0.75 wt% and a 1.5 wt% poloxamer:poly(acrylic acid) polymeric network was introduced into rat nasal passages. The clearance of the formulation from the nose was determined by spectrofluorometry. The fluorescein concentration in the plasma was determined by high pressure liquid chromatography. An intravenous treatment of fluorescein was used as the control. The clearance rate and bioavailability a function of time, post instillation, are shown in Table 18.

Table 18.

Treatment	$T_{1/2}$ (min)[1]	AUC (1-120 min)	bioavailability (%)
IV (control)	-	5765	100
0.75 wt% formulation	20	1060	18
1.5 wt% formulation	50	1915	33

[1] $T_{1/2}$ = time to clear 50% fluorescein from nose

The results indicate a high level of availability of fluorescein using nasal delivery. The results also indicate the effect of poloxamer:poly(acrylic acid) polymer concentration on the effectiveness of the nasal formulation. Increasing concentration levels of polymer increase the clearance time from the application site and the bioavailability of the active agent to the host. Yet other parameters may be considered, such as ease of administration, spraying, etc., which will be apparent to those skilled in the art.

Example 40. The following example demonstrates the ability of the polymeric network to delivery peptides via the nasal route.

Five milliliters of a 5.5% solution of the polymeric network, containing 100 ug of a GnRH analog, was delivered with a syringe through a blueline umbilical

cannula which had been inserted into the nostril of sheep to a depth of 10 cm. Serum concentrations of luteinizing hormone (LH) were determined as a function of time after the nasal administration of the peptide.

The measured serum concentrations of LH are presented in Figure 31. The maximum concentration of the LH was approximately 40 ng/mL, and the maximum response was observed approximately 3 hours post-administration. These results demonstrate that the polymeric network was an effective vehicle for delivering a peptide across the nasal mucosa as evidenced by the stimulated release of luteinizing hormone.

These results indicate the utility of the polymeric network in delivering bioactive materials for local and systemic effects via the nasal route. Its usefulness in delivering peptides across the nasal mucosa overcomes the significant disadvantages of oral delivery of such macromolecular materials. It further circumvents the less consumer friendly route of parenteral administration.

Example 41. The ability of the polymeric network to retain the formulation at the site of application and to prevent roll back in nasal passages is illustrated in human volunteers.

A blind double crossover study was performed on five human volunteers. A nasal formulation was prepared using a 0.8 wt% poloxamer:poly(acrylic acid) and 0.025 wt% oxymetalzoline. A 3 wt% PVP K-29 with 5% PEG 1450, commercially available as Afrin® nasal spray (Schering Plough) was used as a comparison nasal formulation. A 150 μl dose of each formulation was administered to the volunteers.

The volunteers were also asked to comment on the bitterness of the formulation. In a blind double crossover experiment, four of the five volunteers reported no bitter aftertaste (roll-back) in the poloxamer:poly(acrylic acid) polymeric formulation, whereas all volunteers reported a bitter aftertaste in the Afrin® product.

Example 42. This example demonstrates the ability of the polymeric network to control the transit of formulations through luminal tissues. For example, there is great interest in controlling the release of drugs, i.e., with regard to location

of release, as a formulation passes through the gastrointestinal tract. The two previous residence time studies show the ability of the polymeric network to hold the formulation at the site of immediate application. The following example, on the other hand, shows the passage and clearance of a volume of liquid that contains the polymeric network and that has been taken internally via the oral route.

The formulation in Table 17 was once again radiolabeled with the 99m-Technitium(Tc)- DTPA complex. A 5 mL aliquot of the formulation was administered orally via a syringe to three healthy male subjects at two occasions. The presence of the radioactive label in the esophagus was monitored by scintigraphy.

The amount of the formulation that was retained in the esophagus as a function of time is presented in Figure 32. About 65% of the formulation passed into the stomach within 5 seconds, which is about the time that it takes for a solid control to clear through the esophagus. However, up to 15 % of the formulation was retained in the esophagus for 10 minutes. It was also observed that the polymeric formulation coated the lower third of the esophagus. This is compared to a sucralfate suspension (a pharmaceutical agent having pepsin-binding and antacid effects), which had a total retention time of 1-2 minutes.

Example 43. This example demonstrates the utility of the polymeric network in delivering medicaments and drugs to and across mucosal tissue. The example demonstrates vaginal delivery of a steroid hormone.

The test formulations were a 5.5% polymeric network solution containing 60 ug estradiol in a 5 mL dose, American Home Products' Premarin vaginal suppository, containing 300 ug of estrogen conjugates, and Bristol Myers Squibb's Estrace vaginal cream, containing 300 ug of estradiol. The formulations were administered to five sheep in a double crossover experiment, and the estradiol blood levels were determined by radioimmunoassay. The blood levels of estradiol, following the administration of the test formulations, are presented in Figure 33.

The results show that the formulation with the polymeric network, which contained one-fifth the concentration of hormone as the comparable test formulation,

Estrace, provided equivalent blood levels of estradiol. The lower blood levels of estradiol seen with the Premarin could be a result of Premarin being made up of estrogen, and not solely estradiol, derivatives. The polymeric network formulation was also found to coat the vaginal walls effectively before it set up and gelled. Furthermore, there were no side effects or tissue irritation, and there was no sign of outward leakage of the formulation.

The significant performance features observed from these results are the effective delivery of agents at lower dosing and the absence of leakage of the formulation.

Example 44. Since new ways are needed for delivering peptides and proteins across mucosal surfaces, the value of the polymeric network in creating compositions that promote such transport is further illustrated in the following example of the vaginal delivery of gonadotropin releasing hormone (GnRH) and analogs of it.

GnRH, lupron, and deslorelin were mixed into 5.5% polymeric network solutions at concentrations ranging between 20 and 33 ug/mL. Sheep were treated with an amount equivalent to 100 ug of peptide. The bioavailability of the peptides was measured by monitoring the concentrations of circulating luteinizing hormone (LH). The LH levels in untreated sheep served as the control.

The concentrations of LH following administration of the test formulations are presented in Figure 34. Each formulation caused an increase in the LH levels, with the most significant increases arising from the administration of deslorelin. Both deslorelin and lupron provided increases in the LH levels that persisted at least eight hours. These results demonstrate that the polymeric network is effective in delivering peptides across the vaginal mucosa.

Example 36 demonstrated the ability of the polymeric network to solubilize hydrophobic materials. That example, in conjunction with the vaginal delivery of estradiol (Example 43), demonstrate the value of the polymeric network in formulating and delivering more hydrophobic substances. The value is further demonstrated by the ability of the polymeric network to deliver substances more

effectively, thus allowing for dosing with lower amounts of the bioactive materials. Examples 43 and 44 further demonstrate the ability of the polymeric network to formulate and delivery materials with a wide range of molecular characteristics, such as hydrophobicity-hydrophilicity and molecular weight.

What is claimed is:

1. A pharmaceutic composition, comprising:

a pharmaceutically acceptable carrier, comprising a reverse thermally viscosifying polymer network comprising:

at least one responsive polymer component, said responsive component capable of aggregation in solution in response to an environmental stimulus;

at least one structural component, said structural component exhibiting self-repulsive interactions over use conditions,

said responsive component randomly bonded to said structural component, said polymer network characterized in that it viscosifies in response to said environmental stimulus; and

a pharmaceutically active agent which imparts a pharmaceutic effect, said carrier and said agent disposed within an aqueous-based medium.

2. The pharmaceutic composition of claim 1, wherein the responsive component is comprised of at least on hydrophobic region.

3. The pharmaceutic composition of claim 1, wherein the reversibly gelling polymer network is present in an amount in the range of about 0.01 to 20 wt%.

4. The pharmaceutic composition of claim 1, wherein the reversibly gelling polymer network is present in an amount in the range of about 0.1 to 10 wt%.

5. The pharmaceutic composition of claim 1, wherein the structural component is branched.

6. The pharmaceutic composition of claim 1, wherein the structural component is prepared from a monomer selected from the group consisting of carboxylic acids, acrylic acid, substituted acrylic acid, methacrylic acid, substituted methacrylic acids, vinylcarboxylic acids, vinylsulfonic acids, substituted vinylsulfonic acids, vinylpyrolidone, vinylacetic acid, substituted vinylacetic acid, amines, acrylamides, substituted acrylamides, acrylate esters, substituted acrylate esters, methacrylate esters, substituted methacrylate esters, AMPS, MAPTEC, vinyl pyridine, urethanes, amino acids, thiopenes, nucleotides and ionized forms thereof.

7. The pharmaceutic composition of claim 1, wherein the structural component comprises ionized polyacrylic acid or neutralized polyacrylic acid.

8. The pharmaceutic composition of claim 1, wherein the structural component comprises a copolymer.

9. The pharmaceutic composition of claim 1, wherein the structure component comprises a copolymer of acrylic acid and methacrylic acid.

10. The pharmaceutic composition of claim 1, wherein the responsive component comprises a polyoxyalkylene polymer.

11. The pharmaceutic composition of claim 10, wherein the polyoxyalkylene polymer comprises a block copolymer of different oxyalkylene groups, such that at least one polymer block possesses hydrophilic characteristics and at least one block possesses hydrophobic characteristics.

12. The responsive polymer network of claim 10, wherein the block copolymer comprise polyoxyethylene (POE) and polyoxypropylene (POP).

13. The responsive polymer network of claim 10, wherein the polyoxyalkylene polymer comprises a triblock polymer of polyoxyethylene (POE) and polyoxypropylene (POP) having the formula $(POP)_a(POE)_b(POP)_c$, where a is in the range of 10-50 and b is in the range of 50-70.

14. The pharmaceutic composition of claim 1, wherein the responsive component comprises a nonionic surfactant polymer.

15. The pharmaceutic composition of claim 1, wherein the responsive component comprises a poly(alkyl-co-oxyalkylene) having the formula R-$(OCH_2CH_2)_n$-OH, where R is an alkyl group.

16. The responsive polymer network of claim 1, wherein the responsive component is selected from the group consisting of cellulosic, cellulose ethers and guar gums.

17. The pharmaceutic composition of claim 1, wherein the polymer network comprises a plurality of poloxamers.

18. The pharmaceutic composition of claim 1, wherein the polymer network comprises a plurality of poloxamer components randomly bonded to the structural polymer backbone.

19. The pharmaceutic composition of claim 1, wherein the reversibly viscosifying polymer composition comprises a plurality of poly(acrylic acid) components randomly bonded to a poloxamer component.

20. The pharmaceutic composition of claim 1, wherein the aqueous-based medium is selected from the group consisting of water, salt solutions and water with water-miscible organic compound(s).

21. The pharmaceutic composition of claim 1, further comprising an additive selected to increase transition temperature and increase viscosity of the reversible viscosifying polymer network.

22. The pharmaceutic composition of claim 1, further comprising an additive selected to increase transition temperature and decrease viscosity of the reversible viscosifying polymer network.

23. The pharmaceutic composition of claim 1, further comprising an additive selected to increase transition temperature without affecting viscosity of the reversible viscosifying polymer network.

24. The pharmaceutic composition of claim 1, further comprising an additive selected to decrease transition temperature and increase viscosity of the reversible viscosifying polymer network.

25. The pharmaceutic composition of claim 1, further comprising an additive selected to decrease transition temperature and decrease viscosity of the reversible viscosifying polymer network.

26. The pharmaceutic composition of claim 1, further comprising an additive selected to decrease transition temperature without affecting viscosity of the reversible viscosifying polymer network.

27. The pharmaceutic composition of claim 1, further comprising an additive selected to increase viscosity without affecting transition temperature of the reversible viscosifying polymer network.

28. The pharmaceutic composition of claim 1, further comprising an additive selected to decrease viscosity without affecting transition temperature of the reversible viscosifying polymer network.

29. The pharmaceutic composition of claim 1, characterized in that the gel remains translucent to light before and after response to the environmental stimulus.

30. The pharmaceutic composition of claim 1, wherein the poly(acrylic acid) is branched.

31. The pharmaceutical composition of claim 1, wherein said composition further comprises a pharmaceutic agent selected from the group consisting of humectants and emollients.

32. The pharmaceutic composition of claim 1, wherein the pharmaceutic composition takes a form selected from the group consisting of lotions, creams, sticks, roll-on formulations, sprays, aerosols, pad-applied formulations and masks.

33. The pharmaceutic composition of claim 1, wherein the viscosification occurs at a temperature in the range of about 22 to 40°C.

34. The pharmaceutic composition of claim 1, wherein the viscosification occurs at a temperature in the range of about 30 to 37°C.

35 The pharmaceutic composition of claim 1, wherein the pharmaceutical agent is absorbable through skin or mucosal membranes.

36. The pharmaceutic composition of claim 1, wherein the pharmaceutical agent is absorbable through vaginal mucosal membrane.

37. The pharmaceutic composition of claim 1, wherein the pharmaceutical agent is absorbable through nasal mucosal membrane.

38. The pharmaceutic composition of claim 1, wherein the pharmaceutical agent is absorbable through rectal mucosal membrane.

39. The pharmaceutic composition of claim 1, wherein the pharmaceutical agent is absorbable through otic mucosal membrane.

40. The pharmaceutic composition of claim 1, wherein the pharmaceutical agent is absorbable through ophthalmic mucosal membrane.

41. The pharmaceutic composition of claim 1, wherein the pharmaceutical agent is absorbable through esophageal mucosal membrane.

42. The pharmaceutic composition of claim 1, wherein the pharmaceutical agent is absorbable through oral cavity membrane.

43. The pharmaceutic composition of claim 40, wherein the pharmaceutically active agent is selected from the group consisting of miotics, sympathomimetrics, beta-blockers, prostaglandin derivatives, muscarinic antagonists, anti-infectives and carbonic anhydrase inhibitors.

44. The pharmaceutic composition of claim 35, further comprising acceptable antioxidants.

45. The pharmaceutic composition of claim 35, further comprising isotonizing agents.

46. The pharmaceutic composition of claim 35, further comprising a buffer.

47. The pharmaceutic composition of claim 35, further comprising preservatives.

48. The pharmaceutic composition of claim 36, wherein the pharmaceutically active agent is selected from the group consisting of natural and synthetic hormones, anti-fungals, contraceptives, anti-yeast agents, steroids, moisturizers, spermicides, anti-virals, analgesics and anasthetics.

49. The pharmaceutic composition of claim 41, wherein the pharmaceutically active agent is selected from the group consisting of anti-ulcer

agents, sucralfate, H2-blocking agents, antipyretics, analgesics, antacids, antiflatulents, anticonvulsants, antidiarrheals, antifungals, anihypertensives, antihistimines, antiprutitics, antiinfectives, antinauseants, antireflux agents, antispasmodics, contraceptives, hormonals, steroids, cough/cold remedies, diuretics, laxatives, tranquilizers, muscle relaxants, mineral supplements, sedatives, vitamins and mixtures thereof.

50. The pharmaceutic composition of claim 49, further comprising flavoring.

51. The pharmaceutic composition of claim 37, 39 or 40, wherein the pharmaceutical composition is applied in the form of drops.

52. The pharmaceutic composition of claim 37, wherein the pharmaceutical composition is applied as a spray.

53. The pharmaceutic composition of claim 37, wherein the pharmaceutically active agent is selected from the group consisting of decongestants, antihistamines, anti-osteoporosis agents, hormones, antineoplastic agents, Parkinsonism drugs and vaccines.

54. The pharmaceutic composition of claim 48, wherein the reverse thermal viscosifying polymer network is present in a concentration in the range of 0.01-1 wt% of total pharmaceutical composition.

55. The pharmaceutic composition of claim 1, wherein the reversibl thermal viscosifying polymer network is incorporated into a tablet for oral administration.

56. The pharmaceutic composition of claim 1, wherein the pharmaceutic composition is injectible.

57. The pharmaceutic composition of claim 42, wherein the pharmaceutically active agent is selected from the group consisting of anti-ulcer agents, sucralfate, H2-blocking agents, antipyretics, analgesics, antacids, antiflatulents, anticonvulsants, antidiarrheals, antifungals, anihypertensives, antihistimines, antiprutitics, antiinfectives, antinauseants, antireflux agents, antispasmodics, contraceptives, hormonals, steroids, cough/cold remedies, diuretics, laxatives, tranquilizers, muscle relaxants, mineral supplements, sedatives, vitamins and mixtures thereof; and

further comprising flavoring.

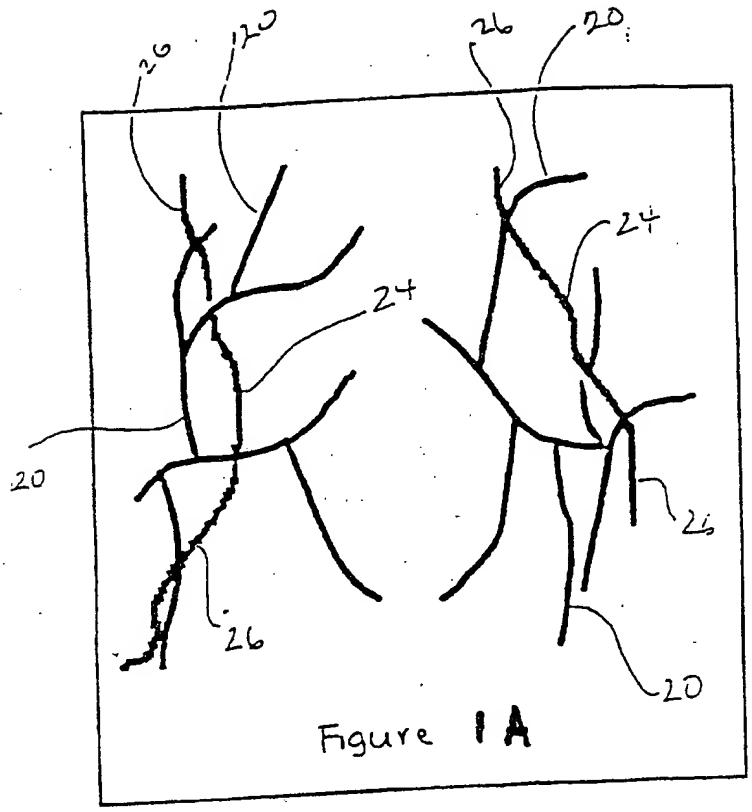


Figure 1A

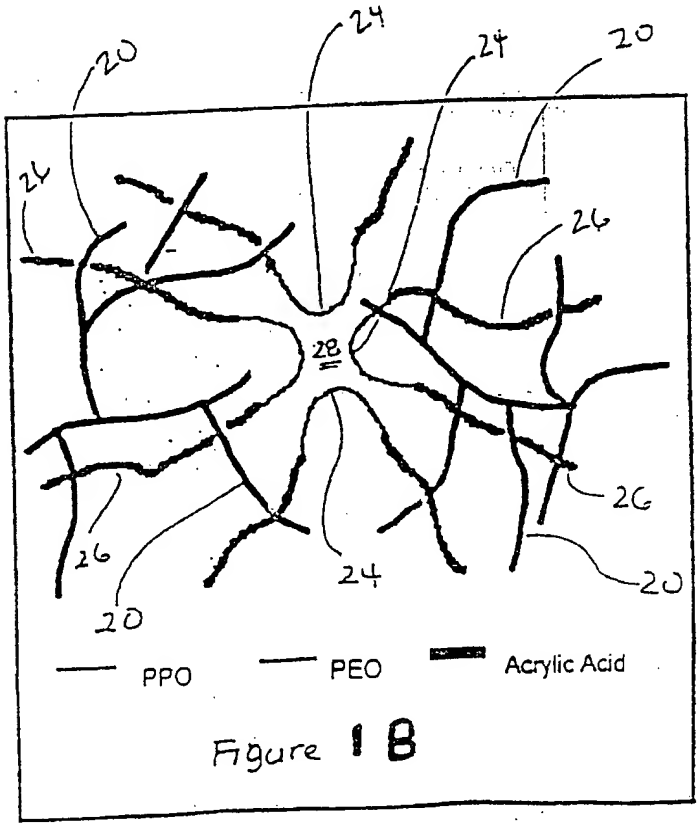


Figure 1B

Figure 2

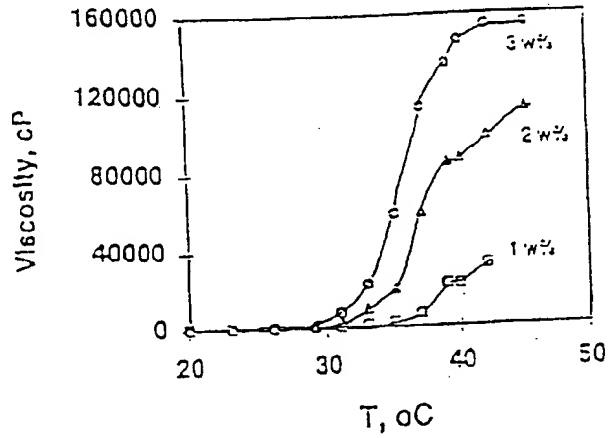


Figure 3

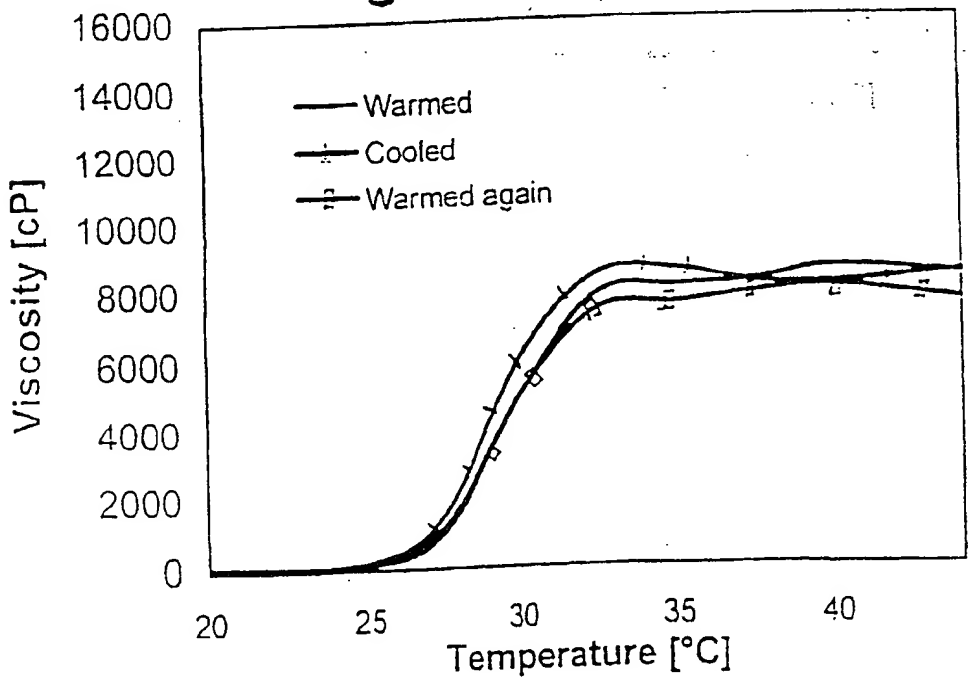
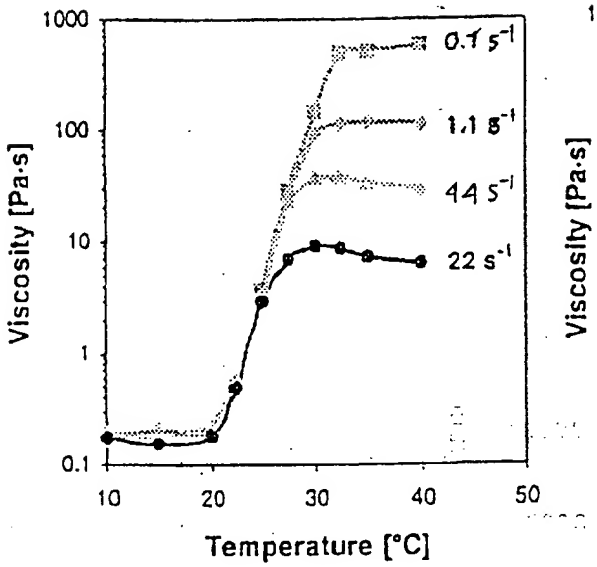
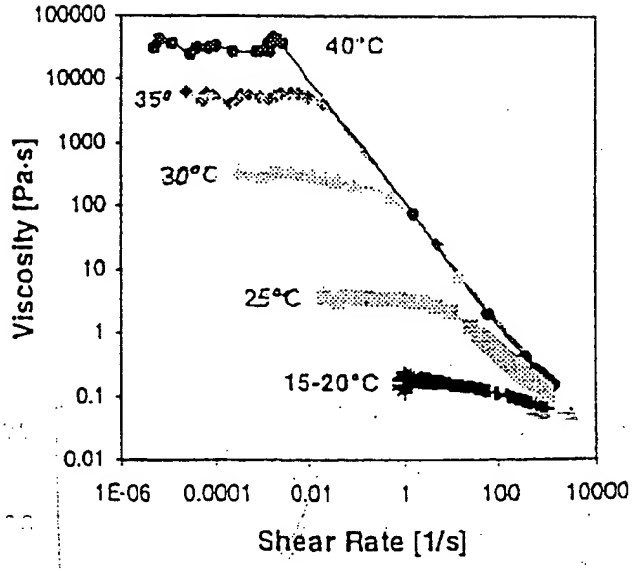


Figure 4A


1000
100
10
1
0.1
Viscosity [Pa·s]
0.1 s⁻¹
1.1 s⁻¹
4.4 s⁻¹
22 s⁻¹
10
20
30
40
50
Temperature [°C]

4B


100000
10000
1000
100
10
1
0.1
0.01
Viscosity [Pa·s]
40°C
35°C
30°C
25°C
15-20°C
1E-06
0.0001
0.01
1
100
10000
Shear Rate [1/s]

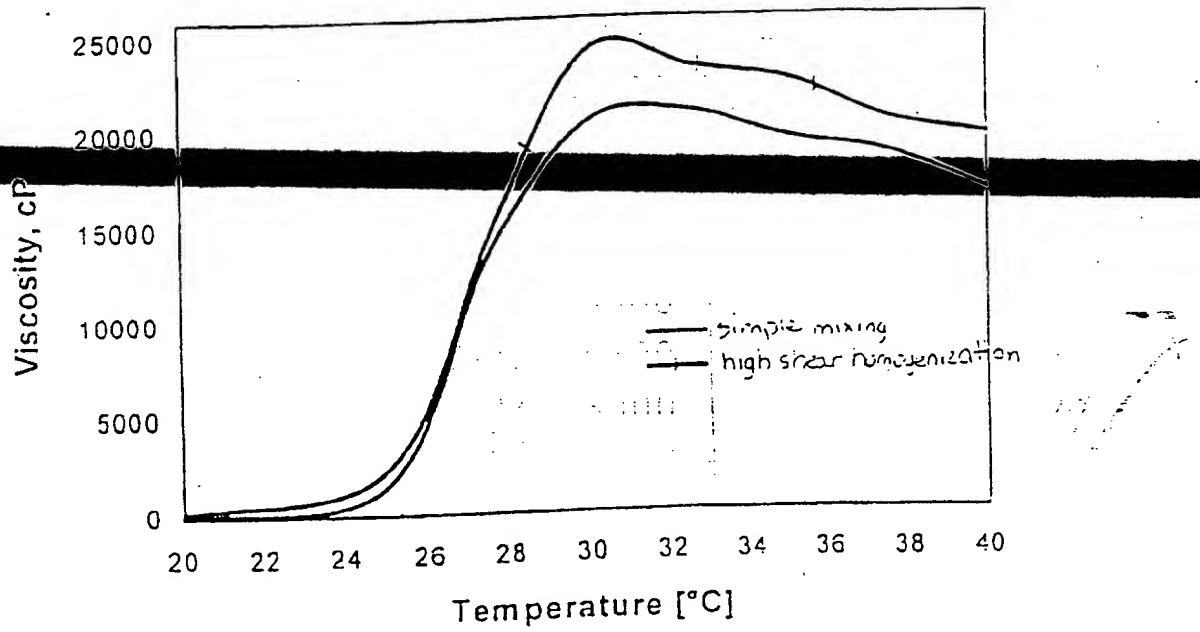

25000
20000
15000
10000
5000
0
Viscosity, cP
20
22
24
26
28
30
32
34
36
38
40
Temperature [°C]
simple mixing
high shear homogenization

Figure 5

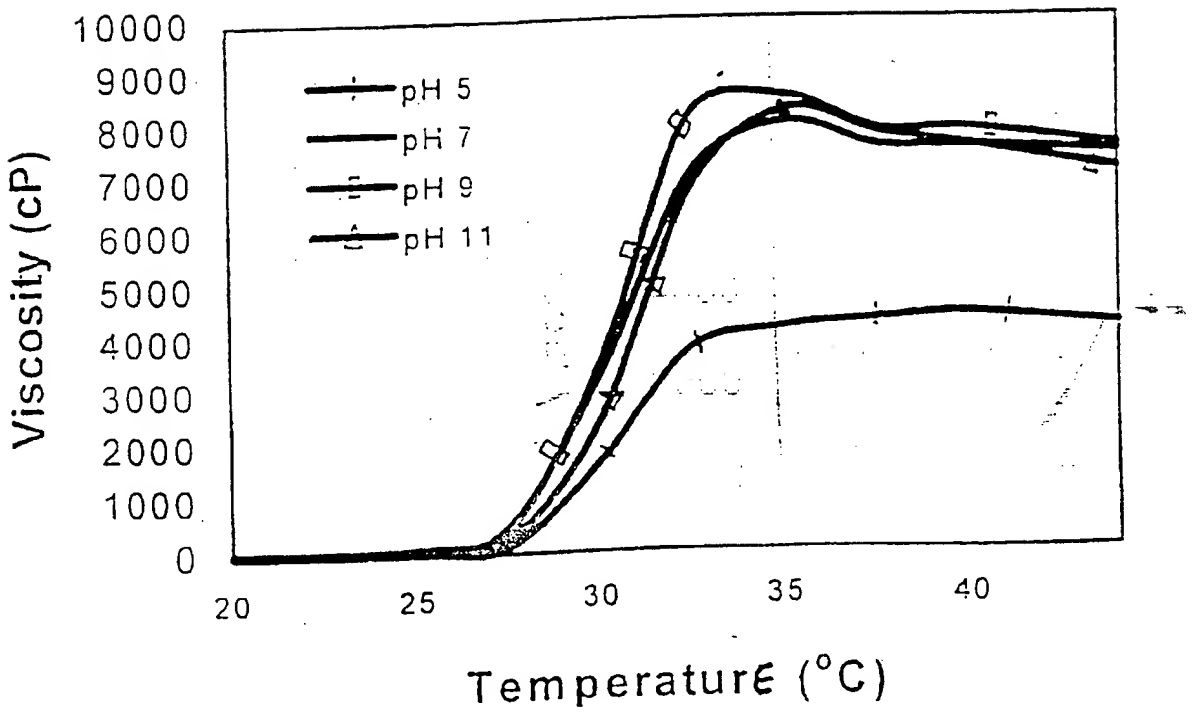

10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
Viscosity (cP)
pH 5
pH 7
pH 9
pH 11
20
25
30
35
40
Temperature (°C)

Figure 6

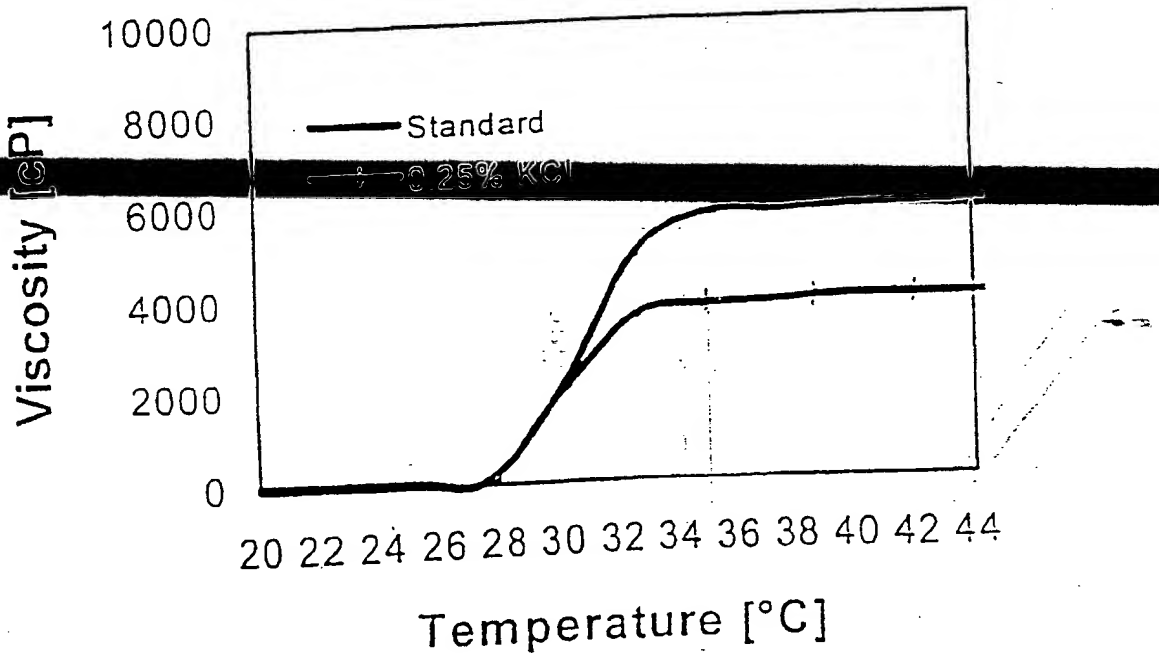

10000
8000
6000
4000
2000
0
Viscosity [cP]
Standard
0.25% KCl
20 22 24 26 28 30 32 34 36 38 40 42 44
Temperature [°C]

Figure 7

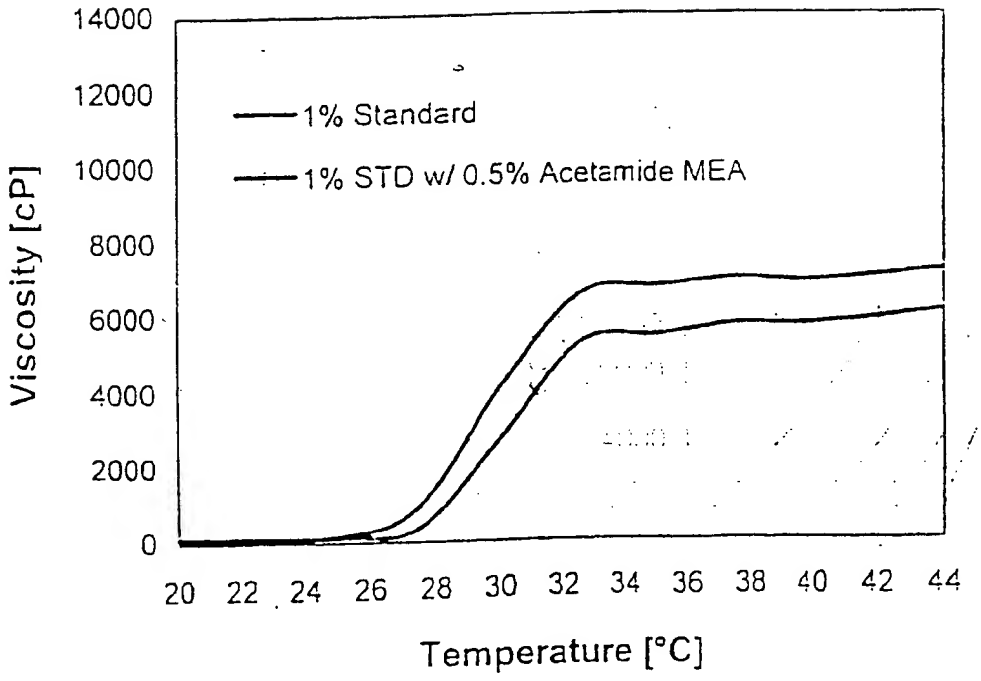

14000
12000
10000
8000
6000
4000
2000
0
Viscosity [cP]
1% Standard
1% STD w/ 0.5% Acetamide MEA
20 22 24 26 28 30 32 34 36 38 40 42 44
Temperature [°C]

Figure 8

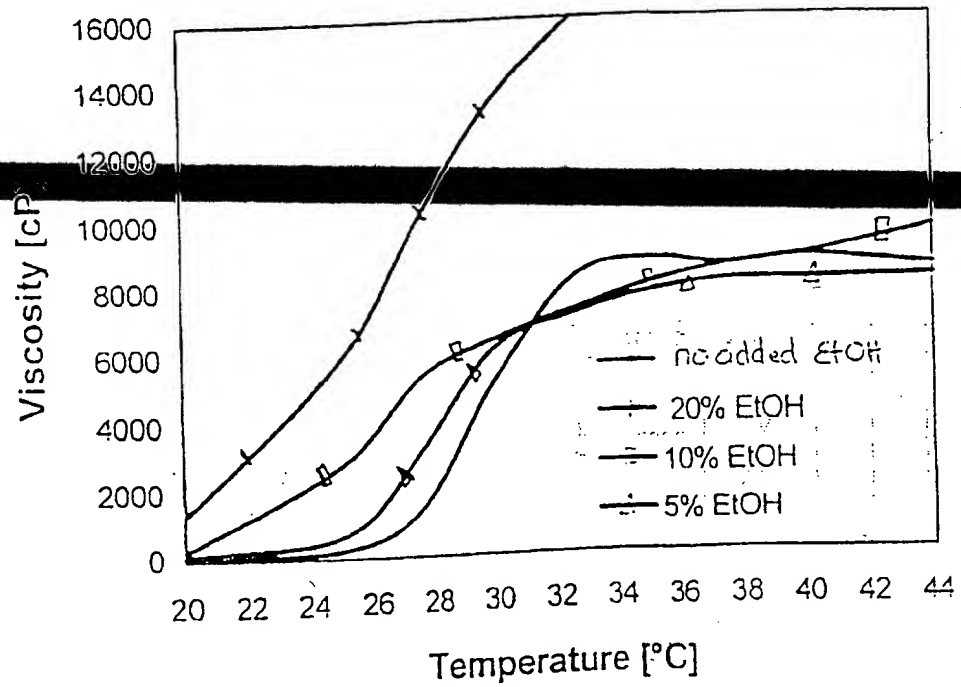

16000
14000
12000
10000
8000
6000
4000
2000
0
Viscosity [cP]
20 22 24 26 28 30 32 34 36 38 40 42 44
Temperature [°C]
no added EtOH
20% EtOH
10% EtOH
5% EtOH

Figure 9

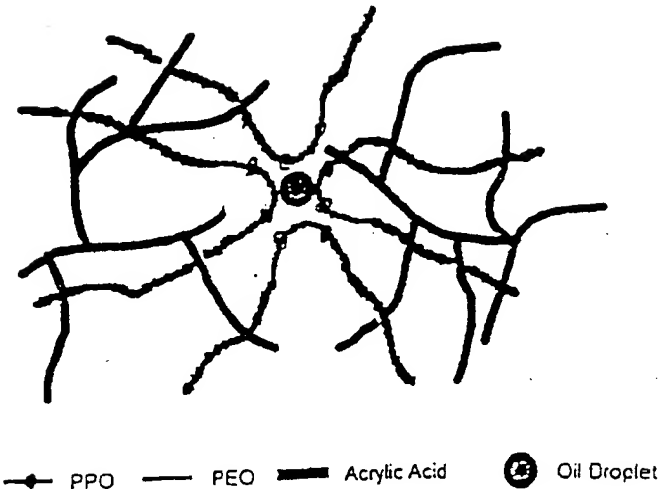


Figure 11

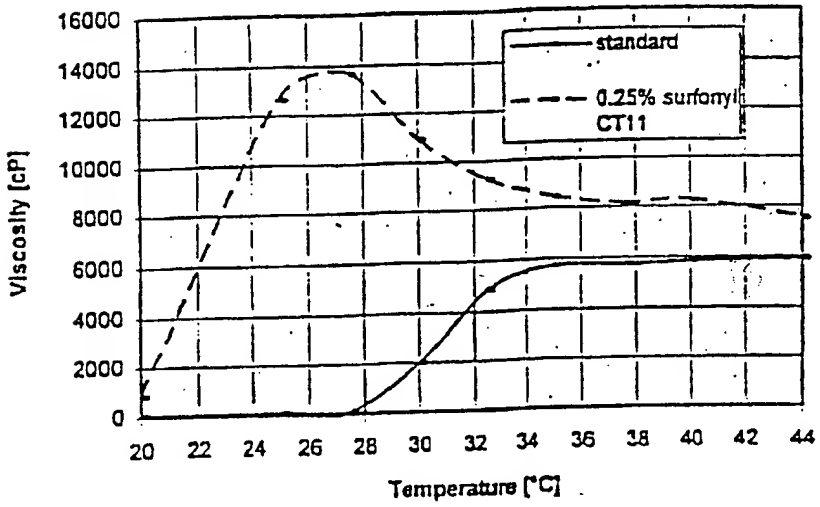
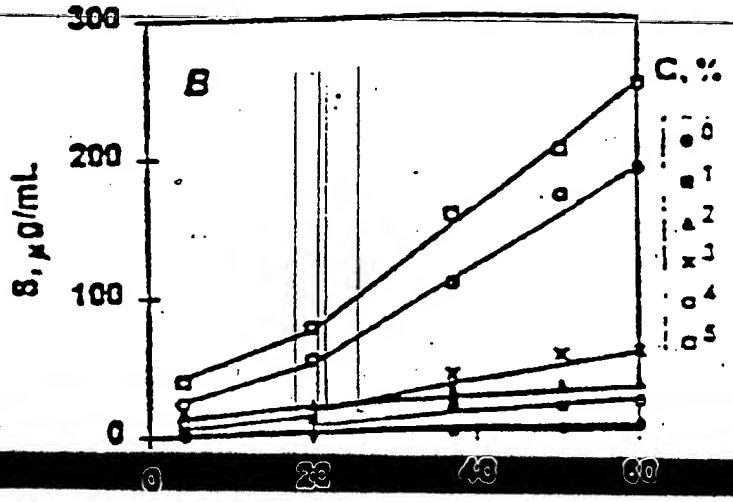


Figure 10

Figure 12

A


300
200
100
0
B
C, %
0
1
2
3
4
5
0
20
40
60

B

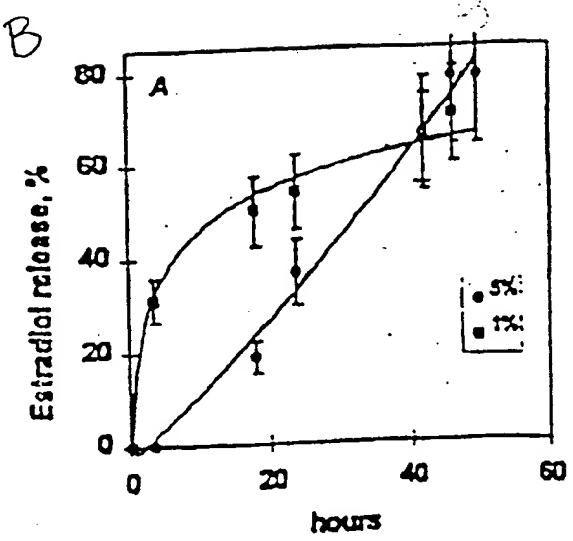
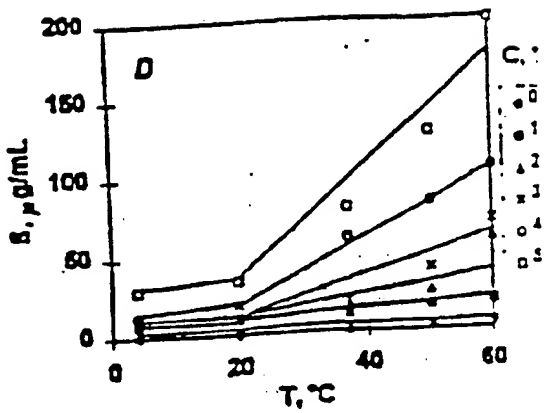

80
60
40
20
0
A
Estradiol release, %
0
20
40
60
hours

Figure 3

A


D
S, μg/mL
T, °C
0
20
40
60
0
50
100
150
200

B

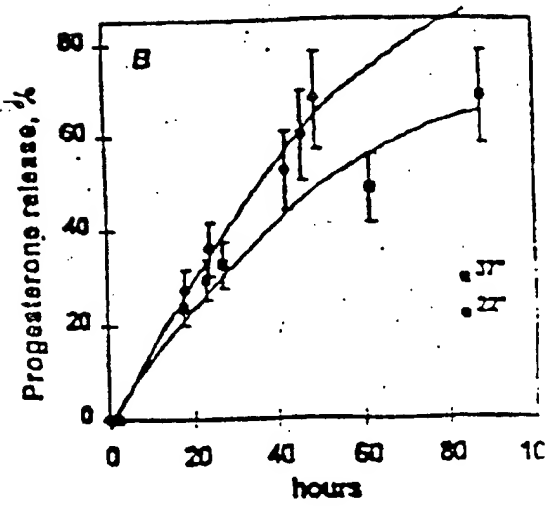

B
Progesterone release, %
hours
0
20
40
60
80
0
20
40
60
80
100

Figure 14

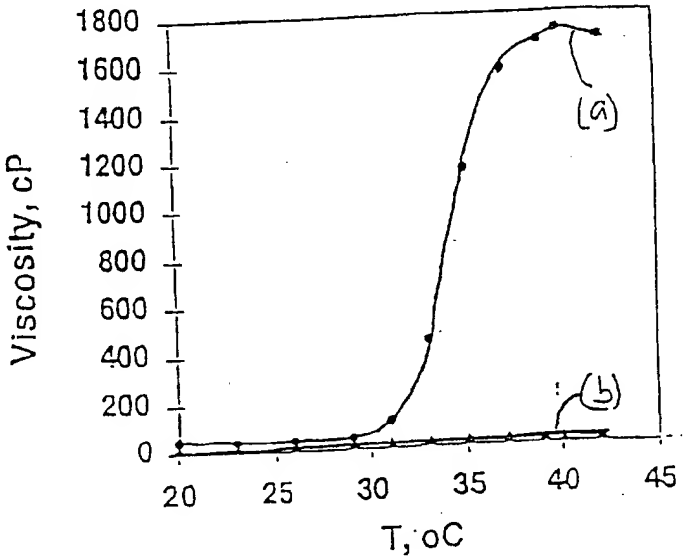


Figure 15

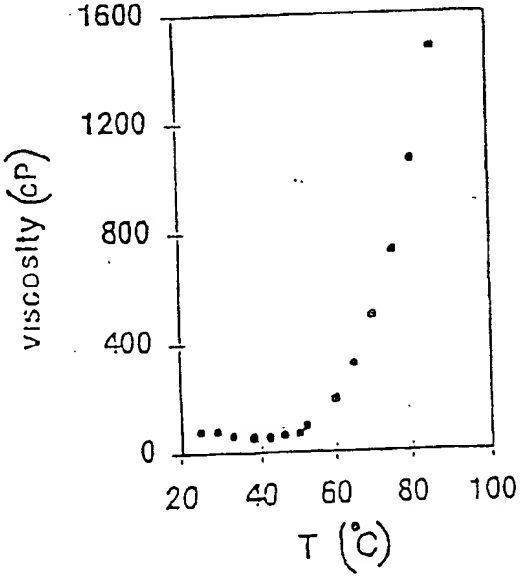


Figure 16

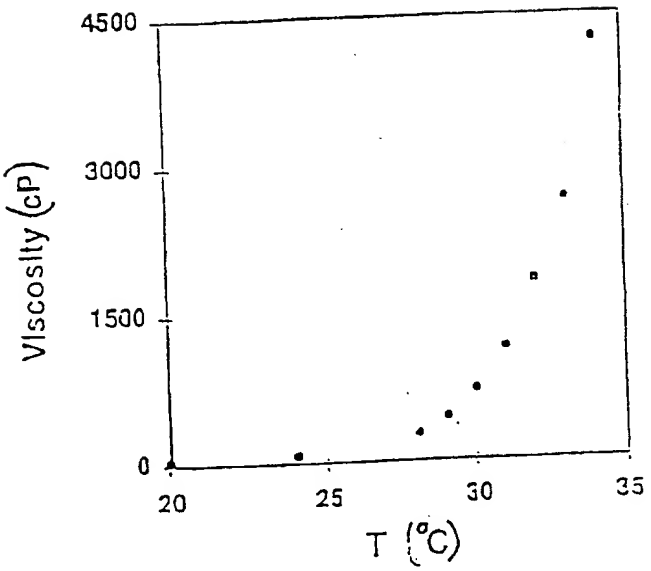


Figure 17

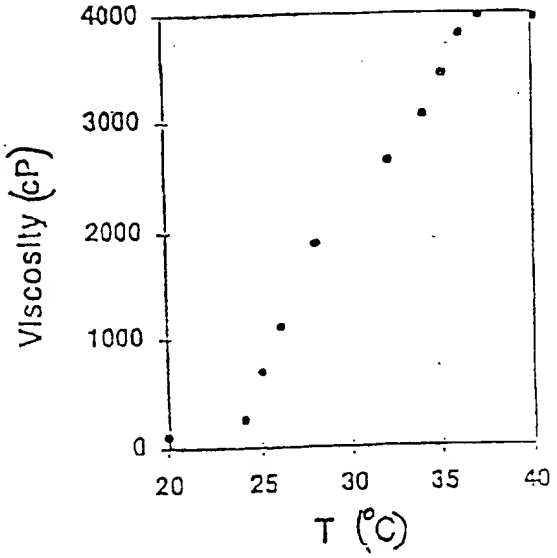


Figure 18

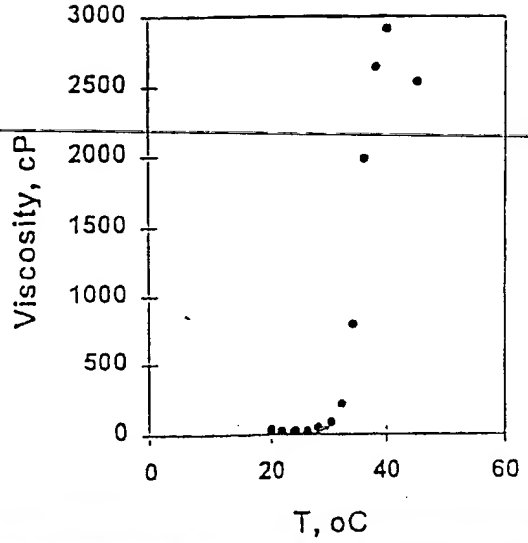
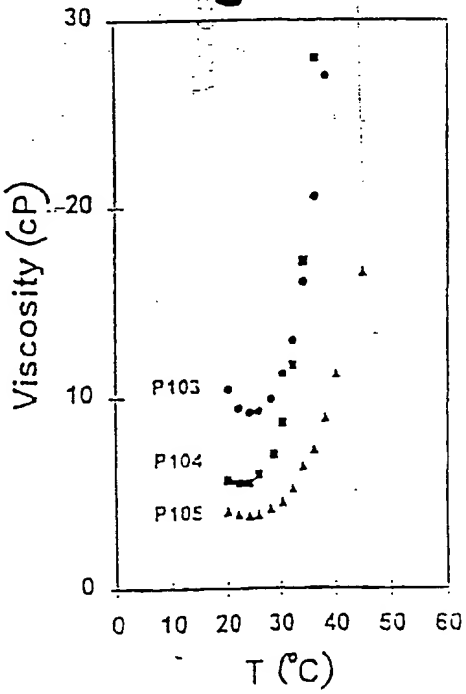


Figure 19



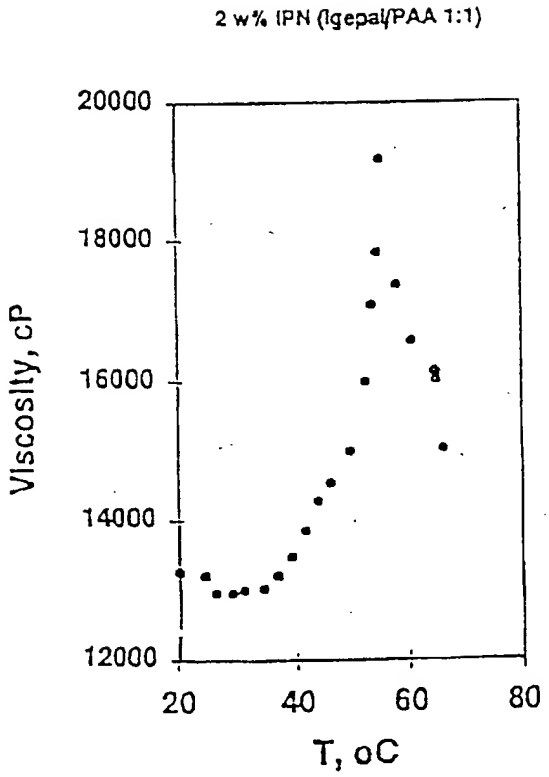

2 w% IPN (Igepal/PAA 1:1)
20000
18000
16000
14000
12000
Viscosity, cP
20
40
60
80
T, oC

Figure 20

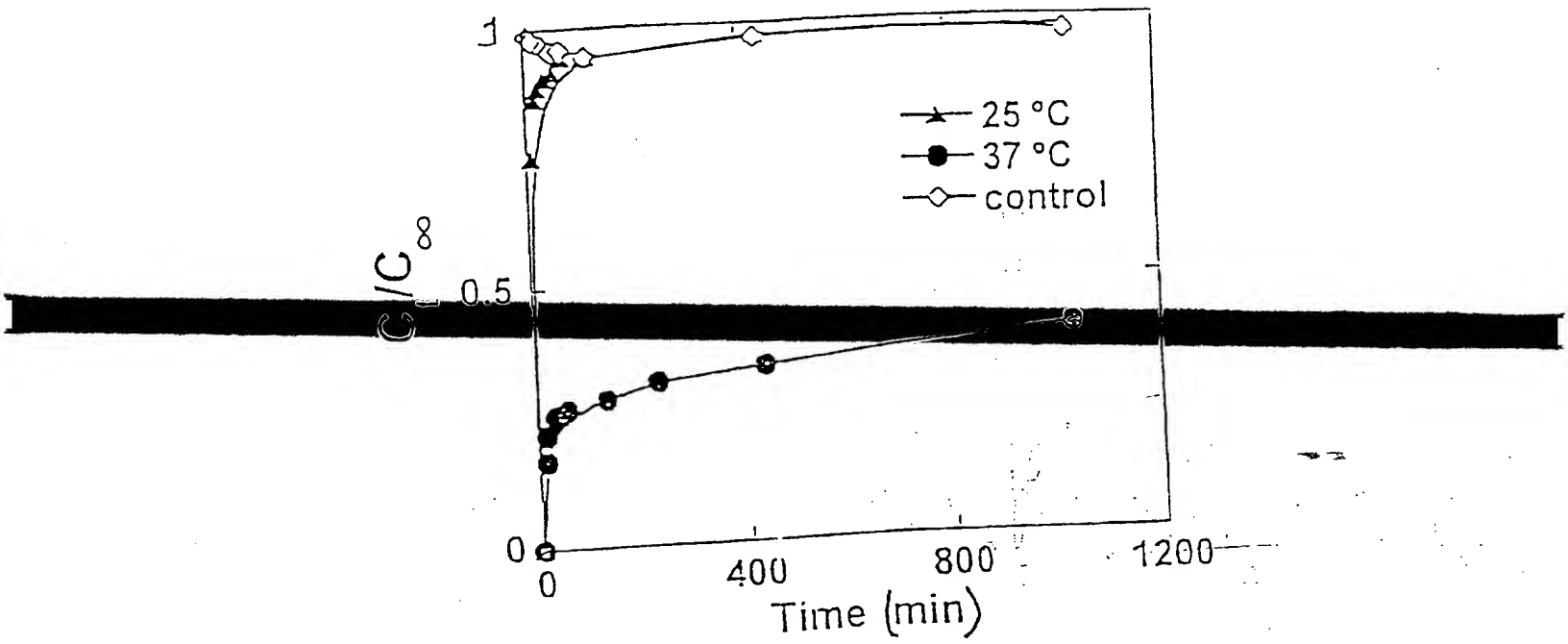


Figure 21

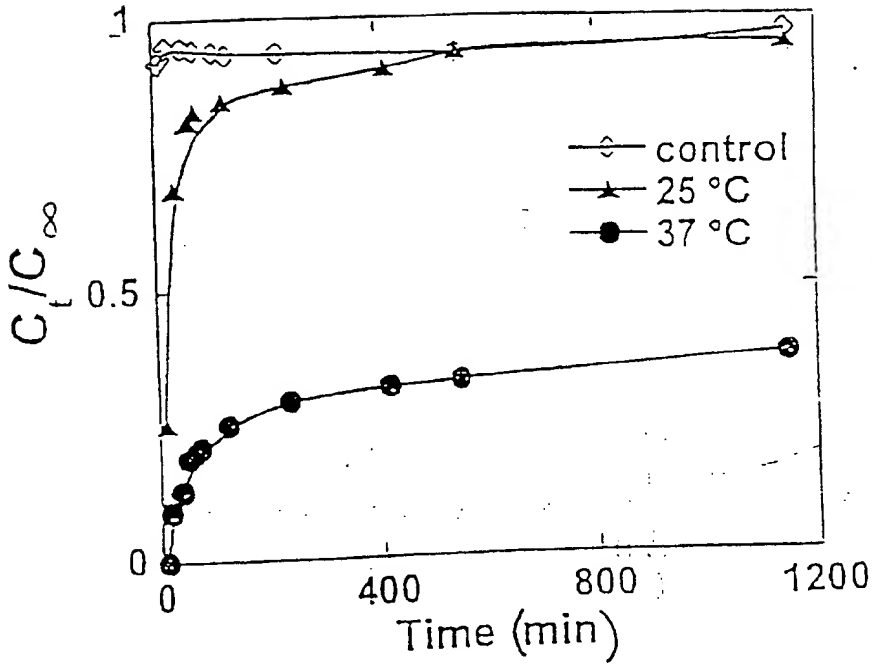


Figure 22

22

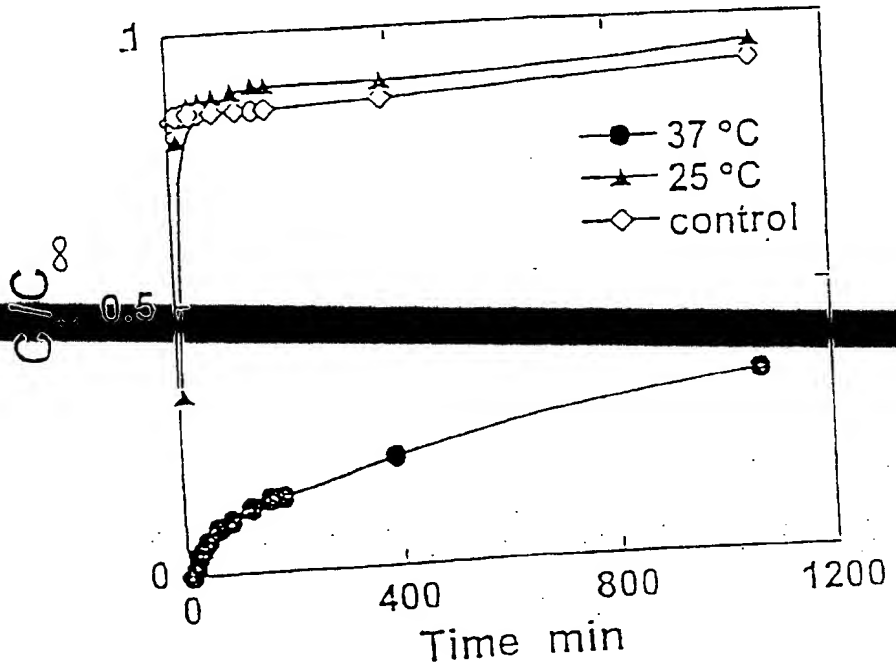


Figure 23

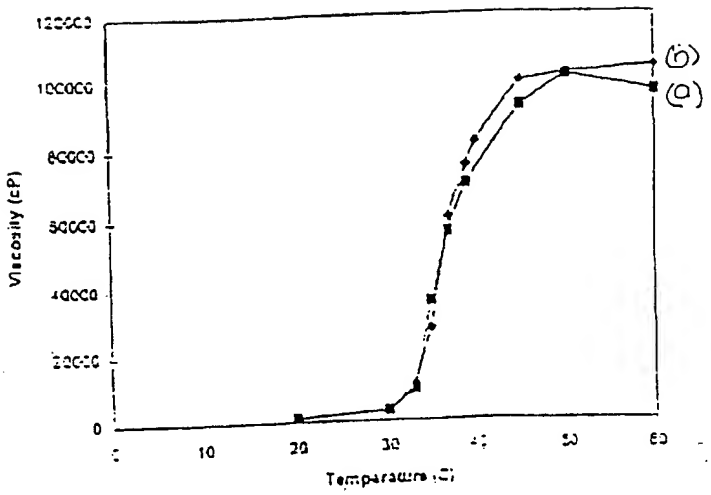


Figure 24

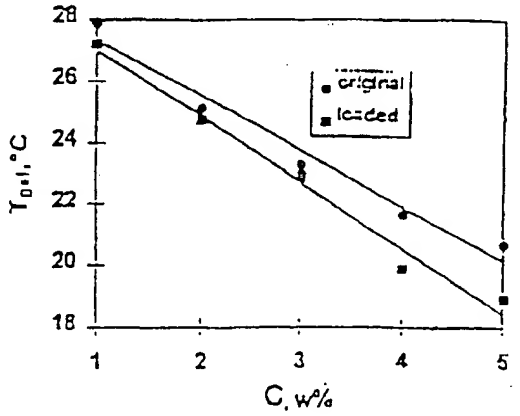


Figure 25

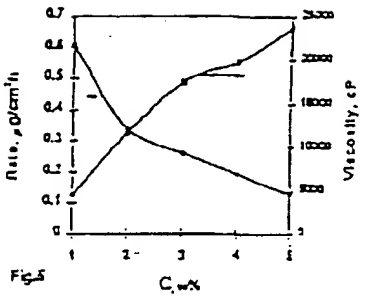


Fig-5

Figure 26

Figure 27

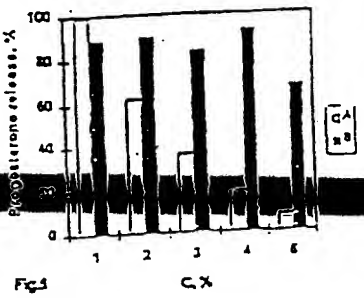
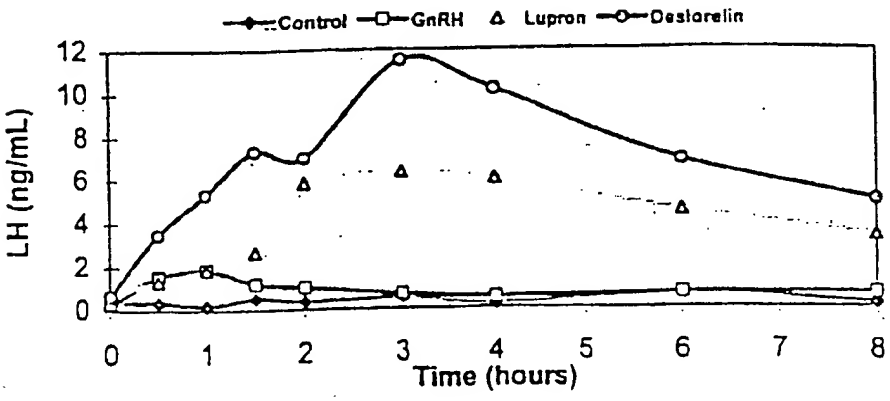


Figure 34



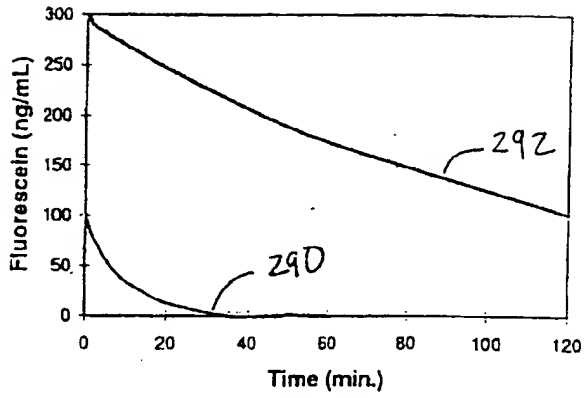


Figure 28

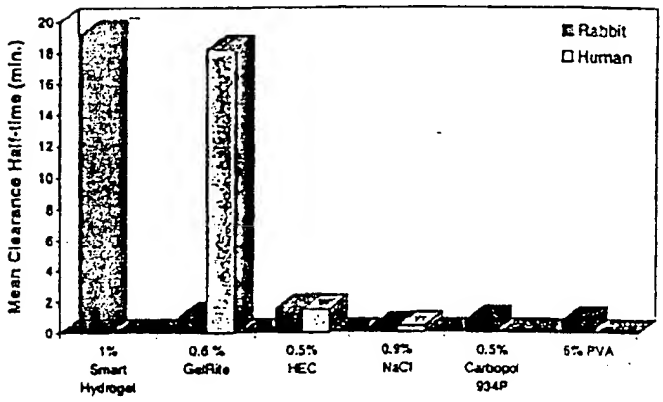


Figure 29

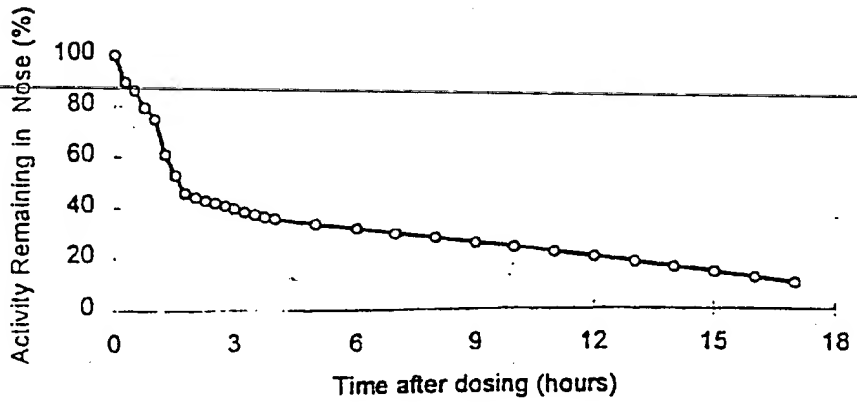


Figure 30

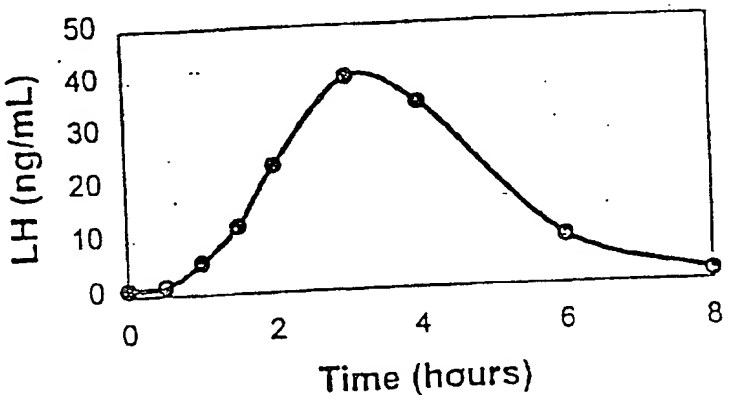


Figure 31

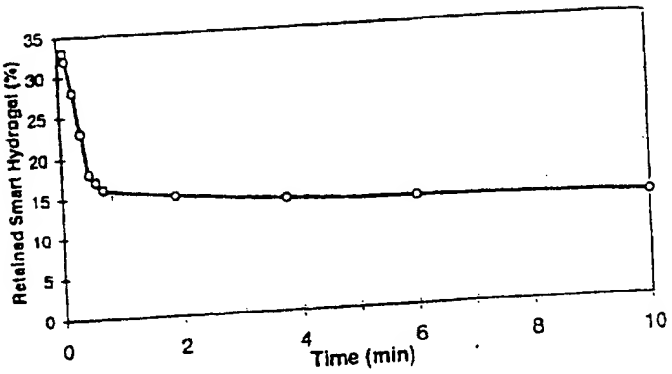


Figure 32

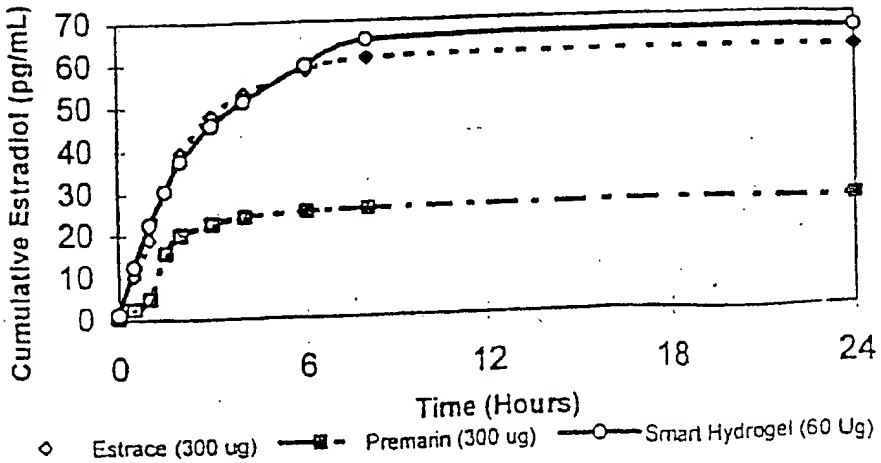


Figure 33